DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 21-272

Sponsor: United Therapeutics Corp.

Submission: (16 October 2000) Request for marketing approval for UT-15 (uniprost, remodulin), for the treatment of pulmonary arterial hypertension.

Review date: March 20, 2001

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Summary: UT-15 was the subject of a development program for pulmonary hypertension in a population somewhat broader than that for which epoprostenol (Flolan) is approved. UT-15 has some potential advantages over Flolan in that UT-15 is administered by subcutaneous infusion, rather than a central line. UT-15 did not meet its primary end point in the pivotal portion of its development program, probably because its effects on exercise tolerance are smaller than expected. UT-15 doses rise progressively with time of exposure; the explanation for this is not known. The use of UT-15 is limited by tolerance to pain and local reaction at the site of infusion. There are no other safety issues, but UT-15 probably lacks Flolan's apparent benefits on mortality.

Distribution: NDA 21-272

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1 Materials utilized in the review

1.1 Materials from NDA/ IND

No reference was made to the IND during the course of this review.

Materials from the NDA that were utilized for this review are listed in the table below.

Submission	Description
16 October 2000	Original NDA submission
03 November 2000	Clinical amendment
16 November 2000	Clinical amendment
05 January 2001	Clinical amendment
11 January 2001	Clinical amendment
15 February 2001	120-day safety update

In addition to the documents, the electronic data supplied by the sponsor were used in this review.

1.2 Related reviews or consults

Not applicable.

1.3 Other resources

Not applicable.

2 Background

2.1 Indication

The proposed indication for UT-15 is for the treatment of primary or secondary pulmonary hypertension:

> *"Remodulin™ is indicated for the long-term subcutaneous treatment of Pulmonary Arterial Hypertension in NYHA Class II, III, and IV patients."*

2.2 Information from pharmacologically related agents

UT-15 bears some structural similarity to Flolan (epoprostinol). The two also share an apparent mechanism of action.

2.3 Administrative history

This development program was managed under IND 36,704 (opened 15 April 1991). The application was inactive from 1992 to 1997. The Division last met with the sponsor in 20 February 1998 for end-of-phase-II discussions of the design of pivotal studies[1]. There was a pre-NDA meeting 15 November 1999. Since filing the NDA, the Division met with the sponsor 8 December 2000 to discuss possibly taking UT-15 before the Cardio-Renal Advisory Committee and 25 January 2001 to discuss clinical review issues.

UT-15 is not approved for marketing in any country.

2.4 Proposed labeling

Labeling is reviewed fully in section 7 (page 33).

2.5 Other background information

Not applicable.

[1] *Tolerance was discussed at that time.*

3 Microbiology, pharmacology, chemistry, biopharmaceutics, and inspections

3.1 Microbiology

In the microbiology review, dated10.24.00, Dr. Langille concluded that the NDA was approvable pending resolution of five specific deficiencies noted on page 17 of his review, for which additional information was requested from the sponsor.

3.2 Chemistry

In the review of Chemistry, Manufacturing, and Controls, dated 8.27.00, Dr. Advani concluded that the NDA was approvable pending information on five specific deficiencies, listed on page 3 of his review, for which additional information is being sought.

3.3 Pharmacology

In the review of Pharmacology and Toxicology, Dr. Joseph commented on several critical aspects of UT-15 pharmacology and toxicology, summarized below and discussed in greater detail in his review. He concluded that 'there are no approvability issues for UT-15 based on the non-clinical toxicity-testing program.'

3.3.1 Pharmacokinetics and metabolism

UT-15 was cleared rapidly in all animal species following administration, with a terminal T1/2 of 20 minutes. Radioactively-labeled UT-15 accumulated in tissues, with the longest T1/2 being fat (478 hours). The feces were the major route of elimination for UT-15 in rats, with 14% of dose excreted in urine and 82% in feces. In contrast, in humans found that the primary route of excretion for the radioactive label (measuring intact drug and metabolites) was urine (79%) and not feces (13%).

Microsomal preparations from human liver showed no significant inhibition of the activities of any of the P450 isozymes (CYP 1A2, 2C9, 2C19, 2D6, 2E1, 3A).

The route(s) of metabolism for UT-15 has not been well-characterized in man. Metabolites identified are the products of oxidation and glucuronidation. The activity of these metabolites has not been determined. See the review, Figure 9, page 32, for proposed metabolic pathway.

In vitro, UT-15 was found to be heavily protein bound in human plasma (91%).

Per the reviewer, UT-15 produced dose-dependent decreases in PR and QRS intervals with no effect on QTc.

3.3.2 Pharmacodynamic effects

In animal models and/or *in vitro*, UT-15 has at least three relevant pharmacodynamic effects: inhibition of platelet activation, vasorelaxation, and inhibition of smooth muscle cell proliferation.

- The inhibition of platelet activation occurs at a IC50 of 13.5 ng/ml for the free UT-15. Since UT-15 is heavily protein-bound (at least in man), this concentration of free UT-15 is appreciably higher than the concentrations anticipated in the clinical setting.
- UT-15 causes vasorelaxation in a dose-dependent fashion and lowers pulmonary arterial pressure in animals. First, UT-15 causes vasorelaxation in a dose-dependent manner on *ex vivo* muscle strips. In animals, doses of as little as 0.4 µg/kg/min in anesthetized rats, administered IV lowered mean arterial pressure. This dose-dependent effect of IV UT-15 was seen in rabbits, cats and dogs as well. The effect of subcutaneous UT-15 was

examined in rats, where a dose-dependent reduction in BP was seen (see table 4 in Pharm/Tox review). Interestingly, oral doses of UT-15 also lowered blood pressure in rats and dogs.

Regarding changes in central hemodynamics following UT-15, IV doses caused reductions in mean pulmonary artery pressure and pulmonary vascular resistance in hypoxic cats and anesthetized dogs. However, systemic vascular resistance also fell, and the pharmacologist suggested that 'there might be little or no selectivity of UT-15 for the pulmonary or peripheral circulation in the normotensive anesthetized dog.' In this same model, UT-15 had a negative inotropic effect at doses of 1 and 3 μg/kg/min IV, although cardiac output rose at doses ≥0.3 μg/kg/min (presumably as a result of vasodilation).

- UT-15 has an anti-proliferative effect on smooth muscle cells in culture. This effect is related to the production of cAMP by cells exposed to UT-15. It isn't know if this effect is seen in animals exposed to UT-15.

3.3.3 Toxicology/ carcinogenicity

In the chronic toxicology studies, reaction site lesions were the most prominent toxicity. The incidence and severity of these lesions were dose-related, which included erythema, inflammation, and the formation of nodules and/or thickening of the skin. Histologically, these nodules contained edema, hemorrhage, cellulitis and/or fibrosis. Increases in spleen and heart weight were also seen in high-dose male and female rats. Laboratory abnormalities seen at high-doses included reversible increases in white blood cell count (male and female rats) and increased total bilirubin (males rats). At lethal doses in dogs, death resulted from intestinal intussusception and/or rectal prolapse. Histologically, hemorrhage and necrosis of the ileum and rectum were noted.

Carcinogenicity studies were not performed. There was no evidence of mutagenicity or clastogenicity in the standard assays (see the Pharmacology/Toxicology review for details). There was no dose-dependent effect on reproductive parameters or on fetal malformations. In rats, maternal toxicity was see at high doses (450 and 900 ng/kg/min).

3.3.4 Tolerance

The reviewer concluded that tolerance was not demonstrated in the studies submitted, although 'tachyphylaxis' was observed in anesthetized animals. In one dog study (summarized on pages 22-24 of the Pharm/Tox review) continuous infusion of UT-15 predicted a …'close relationship between plasma concentration and the onset of hemodynamic effect'. During continuous infusion for 5 hours, however, the measured decreases in total peripheral resistance (TPR) were maintained, but the decreases in pulmonary vascular resistance (PVR) returned towards baseline. This rise in PVR occurred despite steady-state serum concentrations, suggesting tachyphylaxis for the drug effects on PVR.

3.4 Biopharmacology/ Pharmacokinetics

The Biopharmacology/ Pharmacokinetics reviewers concentrated on two large issues related to the clinical pharmacology of UT-15. The first was PK/PD modeling for the following: the concentration of UT-15, the change in hemodynamics (mean pulmonary artery pressure, PAPm), and the six minute walk distance. The second issue addressed in the review was the possible development of hemodynamic tolerance. See the final Biopharmacology/ Pharmacokinetics review for their final assessment regarding the approvability of UT-15.

3.4.1 Metabolism

The absorption of UT-15 following SC administration is approximately 100%. UT-15 is metabolized in the liver with <4% excreted unchanged in the urine. Five metabolites (of unknown activity) are formed, although the metabolic pathways used have not been identified. As discussed in the Pharmacology and Toxicology review, oxidation and glucuronidation is responsible for several of the metabolites.

3.4.2 Pharmacokinetics

The pharmacokinetics of UT-15 are linear over a dose range of 2.5 to 15 ng/kg/min. The drug follows a 2-compartment body model, with a half-life of 2-4 hours in man. This half-life was not affected by gender, race or obesity. The presence of hepatic impairment significantly increased both the Cmax and the $AUC_{0\text{-}inf}$. Of note, no evaluation of the pharmacokinetics of UT-15 in severe hepatic impairment was performed. Similarly, the effect of renal insufficiency on the pharmacokinetics of UT-15 has not been characterized. This is relevant as 78% of a given dose is excreted in the urine, largely as metabolites, and we lack information about their possible activity.

3.4.3 Concentration-effect relationship of UT-15 to pulmonary hemodynamics and clinical outcomes

Drs. Gobburu and Nguyen concluded that there was a concentration-effect relationship of UT-15 on mean pulmonary artery pressure (PAPm) and other hemodynamic measures and that the slope of the relationship was shallow, suggesting a small effect of UT-15 on hemodynamics over the dose range utilized in the clinical trials. They were also able to conclude that there was a relationship between changes in PAPm and changes in the six-minute walk distance. Again, the slope of the relationship was shallow, suggesting a small effect of UT-15 over the range of doses used in the clinical trials. One explanation for these findings (unproven) is that the free concentrations of UT-15 achieved in the trials were on the low end of the concentration-response curve when compared with the EC_{50} derived from *in vitro* experiments.

3.4.4 Tolerance

The reviewer's have made no written statements with regard to the development of clinical tolerance when this documents was created. In discussions with Drs. Nguyen and Gobburu, they pointed out the difficulty in assessing the development of tolerance in the available clinical data. With regard to central hemodynamic measurements (*e.g.*, PAPm, cardiac output), no study included more than two measures of these values. This seemingly precludes evaluation of tolerance for these parameters.

3.5 Division of Scientific Investigation

The overall evaluation of the inspection reports, performed by Jorge C. Rios, M.D., found that this study was performed well, informed consent was obtained in all cases, only minor protocol violations were noted. Overall, the data were classified as acceptable

4 Description of clinical data sources

4.1 Primary source data

4.1.1 Study type and design

The information in this review includes the results of the two pivotal trials P01:04 and P01:05 as well as 10 smaller studies (P01:01; P01:02; P01:03; P01:02; P01:07; P01: 08; P01:09 and P01:10 P01:11, P02:01, P03:01 and P76:01). The 10 smaller studies enrolled a total of 145 patients that were either normals, patients with pulmonary hypertension, patients with CHF or patients with peripheral vascular disease. The specifics of the studies are summarized in Table 1.

Table 1. Short-term, non-pivotal studies of UT-15

	Type	Demo-graphics	Subjects[2]	Design, duration
P01:01	Acute, dose-range-finding study of iv UT-15 compared to intravenous, (iv) Flolan® in patients with severe Primary Pulmonary Hypertension [PPH]	12-57y; 11F / 4M	15/15	1) Flolan®: dose-ranging to a maximally-tolerated dose (MTD); 2) 90-minute Flolan® washout segment; 3) UT-15 dose-ranging to a MTD; 4) a 90-minute UT-15 maintenance segment (at the MTD); and 5) a 120-minute UT-15 washout segment
P01:02	Acute, dose-range-finding study of a fixed iv dose and subcutaneous (sc) UT-15 doses up to the MTD patients with severe PPH	22-71y; 20F / 5M	30/25	1) 75-minute intravenous infusion of 10 ng/kg/min UT-15; 2) 150-minute washout.; 3) 150-minute subcutaneous UT-15 infusion; 4)150-minute washout.
P01:03	Multicenter, double-blind, randomized (2:1, Active: Placebo), parallel, placebo-controlled 8-week trial in NYHA III/IV PPH	12 - 73 y 21 F/5 M	Total 24/26 Treatment 16/17 UT-15 8/9 Placebo	8 weeks Subcutaneous infusion 2.5 - 50 ng/kg/min
P01:07	Bioavailability of UT-15 in Healthy Volunteers	18 - 49 y; 7F / 8M	15/15	Acute, IV versus sc infusion 15 ng/kg/min for 150 min
P01:08	Effects of Acetaminophen on the Pharmacokinetics of UT-15 in Healthy Volunteers	18-47 y; 17F / 12M	29/29	Acute SC infusion 2 doses of 15 ng/kg/min each
P01:09	Chronic (28 day) Dose-Escalation study of the pharmacokinetics of UT-15 in Healthy Volunteers	23-49 y; 8F / 6M	14/14	Chronic SC infusion Four 7 day infusions at 2.5, 5, 10, and 15 ng/kg/min
P01:10	Mass Balance, Urinary Metabolite Profiling, And Safety Study of [^{14}C] UT-15 in Healthy Volunteers	23-45y; 6M	6/6	Acute SC infusion 15 ng/kg/min for 8 hr (72.5 to 95.7 µCi)
P01:11	Patients transitioning from Flolan® to UT-15	29-54y 3F	—/3	UT-15 administered SC
P02:01	Patients with porto-pulmonary hypertension	25-59 y 3F/6M 1B/8W	12/9	Acute subcutaneous infusion at a rate of ng/kg/min for 150 min.
P03:01	Patients peripheral vascular disease	56-78 3F/5M 1B/8W	8/8	Intravenous dose escalating phase to tolerance . followed by a 120 minute infusion
PP76:01	Patients with CHF class III-IV	Mean age 47 7B/5W	12/12	Dose escalating study every 15 minutes followed by 90 minute fixed infusion

Of these patients, 64 normals were exposed to UT-15 in biopharmaceutical or mass balance studies. The results are included in the biopharm review. The patients who enrolled into the other studies either had pulmonary hypertension, CHF or peripheral vascular disease as their underlying medical problem. None of these studies was sufficiently well designed or sufficiently large to add information with respect to efficacy, dose response or safety of UT-15. Long term safety is derived from study P01:06. This

[2] *Planned/actual*

study allowed for the long-term treatment of patients who were treated either with active UT-15 or vehicle in studies P01:03, P01: 04 or P01:05. In addition a total of 208 patients not previously enrolled into clinical studies were treated in an open-labeled manner.

4.1.2 Subject enumeration and exposure

As of the cutoff date, exposure was 476 subject-years, with 224 subjects treated for more than 1 year. This open-label study comprises the bulk of the exposure to UT-15. The exposure in this study is shown in Figure 1.

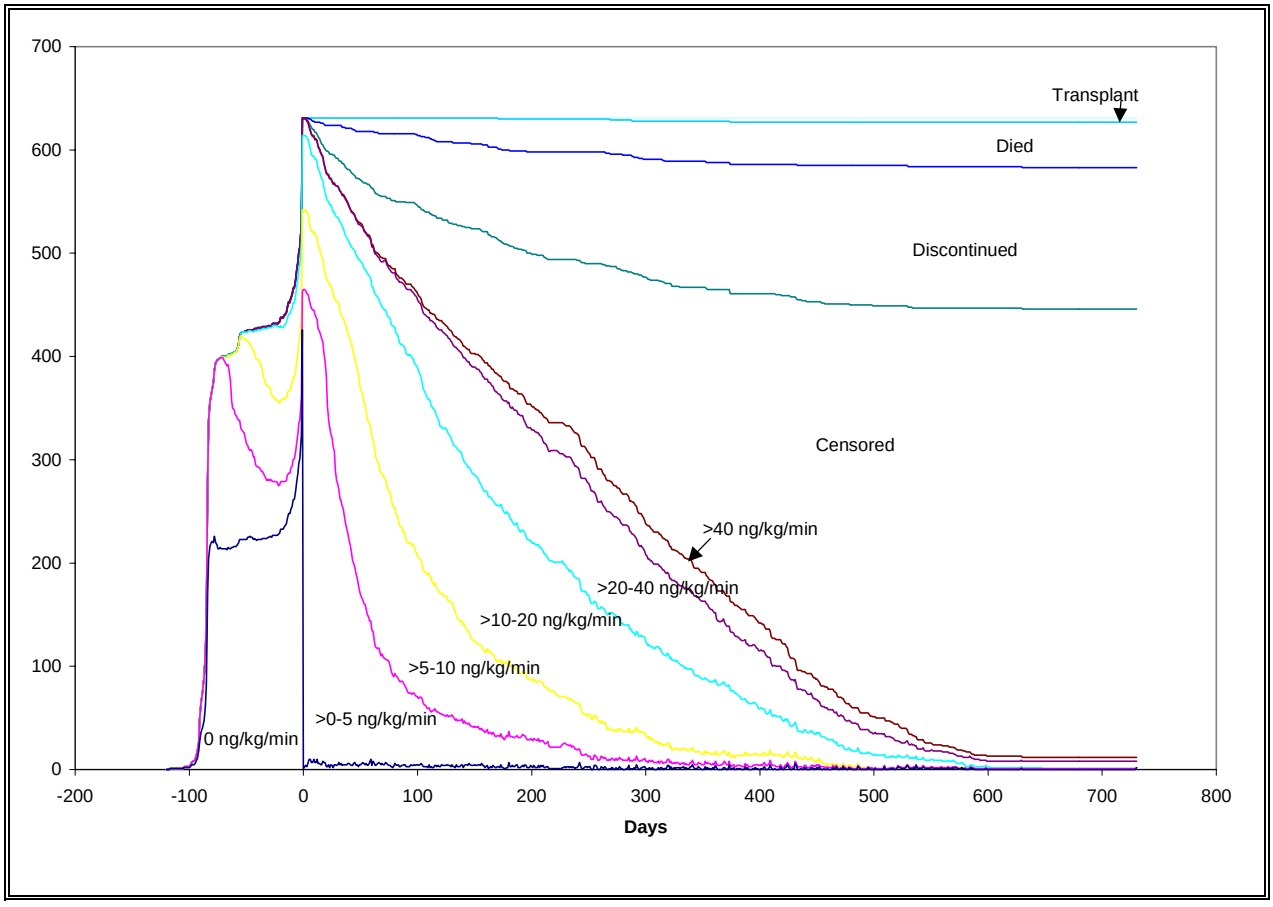

Figure 1. Exposure to UT-15 (P01:06)

Figure is a stacked bar chart in which each subject contributes in one of a number of states on each day after enrollment. Subjects entering from studies P01:03, P01:04, and P01:05 have dosing information prior to enrollment in P01:06. Data obtained from 120-day safety update.

The proportion of subjects who remained alive, in study, and on a non-zero dose of UT-15 is shown in Figure 2.

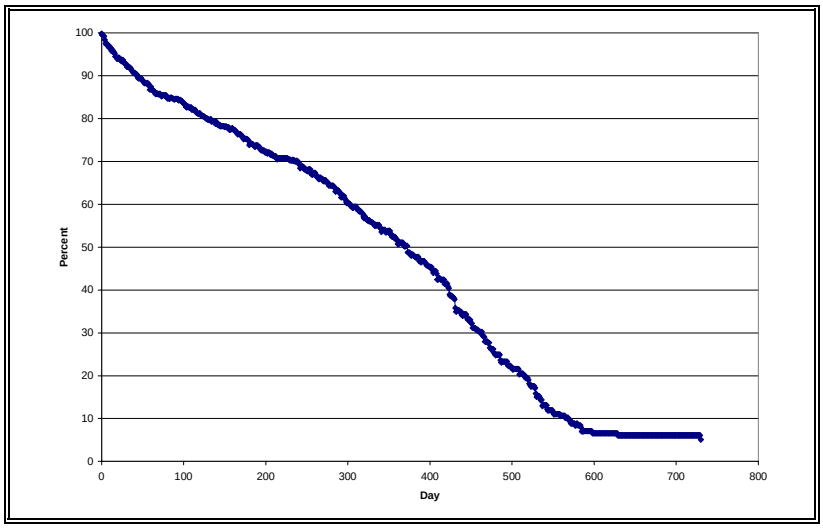

Figure 2. "Life-table" for remaining on UT-15 (P01:06)

Proportion of subjects remaining on a non-zero dose of UT-15 among subjects not censored by the reporting cutoff date. This is not a true life table, because subjects could go to a zero-dose and subsequently return on treatment.

For subjects in study P01:06 who remained on any non-zero dose, the proportion on various doses is shown in Figure 3.

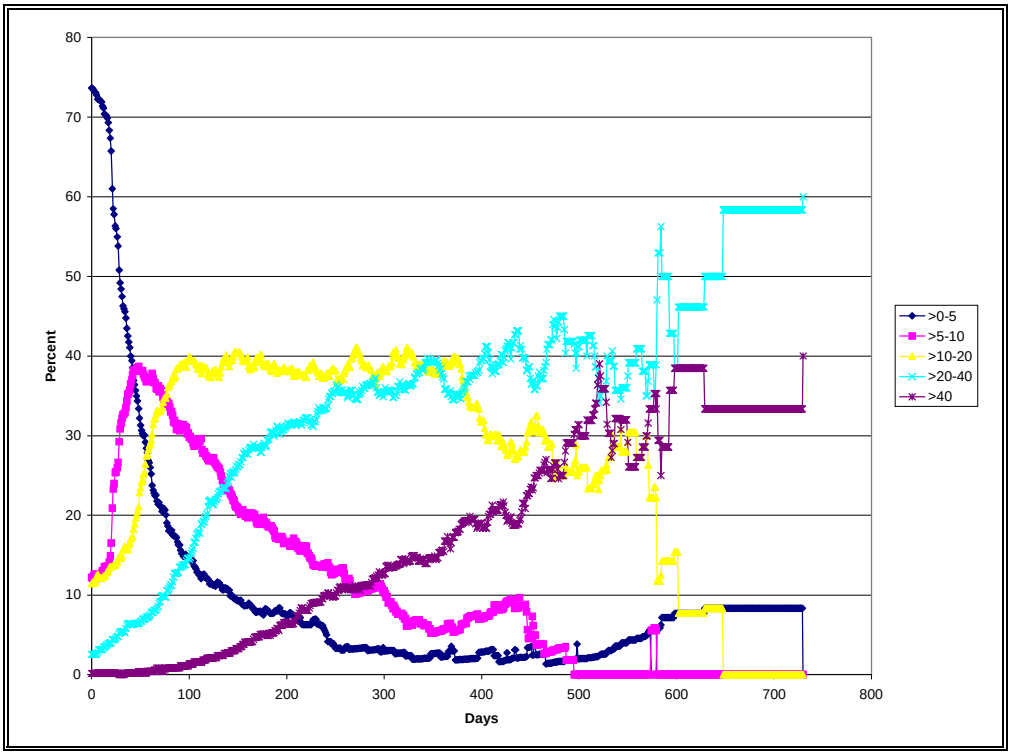

Figure 3. Censored view of dosing (P01:06)

The demoninator is the number of subjects on any non-zero dose. Data from 120-day safety update.

4.1.3 Demographics

There were few males, few non-Caucasians, and few subjects over age 65. No separate analyses were performed in these subgroups.

4.2 Secondary source data

4.2.1 Other studies

There are no other known studies with UT-15.

4.2.2 Post-marketing experience

There is no post-marketing experience with UT-15.

4.2.3 Literature

No publications were found that did not correspond with identified studies.

4.3 Adequacy of clinical experience

The development program appears to have been large enough to have reliably detected a reasonably sized treatment effect. The population studied contained relatively few males and relatively few representatives of racial minorities, but there are no data to suggest such groups respond differently to pulmonary hypertension or to treatments for pulmonary hypertension.

Long-term exposure in approximately 600 subjects or 500 subject-years is adequate to exclude, with 95% confidence, an incidence of unobserved adversity at the rate of about one per 150 exposed patients or one per 125 patient-years. This is rather less safety data than is frequently available for the evaluation of a new chemical entity.

4.4 Data quality and completeness

Case report forms were provided for all subjects who died or were withdrawn for medical reasons. A spot-check comparing values in the CRF with the sponsor's electronic data revealed no discrepancies.

5 Integrated review of effectiveness

Studies P01:04 and P01:05 are the key pivotal studies[3]. The procedures and measurements for these two protocols were identical and the studies were analyzed both individually and as a single pooled study. Subjects who enrolled into these studies were symptomatic pulmonary hypertension subjects (NYHA Class II-IV), despite optimum concurrent therapies. The etiology of the pulmonary hypertension could be either primary disease or could be as consequence of either collagen vascular disease or left to right congenital shunts.

5.1 Six-minute walk

The primary end point was the change in walking distance from baseline at the end of week 12. For the pivotal analyses, missing values for those who discontinued were imputed. Those who discontinued either because of death, deterioration or transplantation received the worst rank or worst value. Those who discontinued due to adverse events had their last rank carried forward or their last metric for walk carried forward.

The primary method of analysis was a non-parametric analysis of the pooled studies. The database was to be considered demonstrating a benefit for UT-15 if either both studies were by themselves significant at the $p< 0.049$ or if one study was significant ($p< 0.049$) and the pooled studies had a p-value of less than 0.01.

By the sponsor's own analysis the database would not be considered successful. Neither of the studies demonstrated a p-value of < 0.049 ($p=0.06$ for both studies), although the pooled studies demonstrated an overall p-value of < 0.01 ($p=0.006$ for the pooled studies]. The magnitude of the change in median walking distance was small, ranging from 2 meters in study P01:04 to 19 meters in study P01:05. The fractional increase in walk distance over baseline for UT-15 patients relative to vehicle was between < 1% to a 6% increase for each or the studies and a pooled increase of approximately 3%.

Not only did the sponsor's analysis not meet the pre-specified criteria for considering the trials a success but also there was an inherent bias in the statistical approach employed in the analysis of the study. There was a clear imbalance in the number of subjects who discontinued for adverse events. Nearly all such discontinued subjects were treated with UT-15 and nearly all those who discontinued did so for infusion site pain or infusion site reaction.

There are several consequences that result from this algorithm for imputing data for discontinued subjects. First, those who discontinue due to adverse events could never be classified as worst outcomes even if they should subsequently die, deteriorate or receive a lung transplant. The fraction of subjects who discontinued for adverse events, therefore, was shielded from the worst imputed outcome values possible in this study.

Second, nearly all subjects that discontinued in the UT-15 group did so because of infusion site pain/ reaction. Since infusion site pain was ubiquitous in the UT-15 subjects, those who discontinued were possibly suffering from infusion site pain in conjunction with a worsening of their pulmonary hypertension. The attribution of cause and therefore the imputed value was markedly dependent on this attribution.

Third, the process of imputation presupposes the values at early times are reflective of the performance at the time of discontinuation. There are clearly subjects whose imputed value for walking distance does not reflect their status at the time of discontinuation. Subjects who discontinue for pain, whose discontinuation fell within

[3] *For a full description, see Section A.4 on page 82.*

the time-window of an exercise test and who did not undergo testing were imputed an earlier value, which would likely be better than their current status.

Lastly, there was an asymmetry in the need for pain medication that could alter vascular dynamics or mitigate some of the disease symptoms particularly those that are associated with pain.

In order to deal with the inherent biases due to the unequal rates of discontinuation for adverse events the data was analyzed in three additional ways. The first analysis included as worst outcomes three UT-15 and two vehicle subjects who died or were transplanted during the 100-day window of the study. The resulting p-values of the pooled database to 0.02 and that for the individual studies to >0.1.

The second analysis further includes as worst outcome, those subjects who discontinued for adverse events if Flolan® was started within one month of discontinuation and within the window of the study. There were six additional subjects. Two subjects were started on Flolan® either prior to or immediately upon discontinuation of UT-15. Two additional subjects were started within two weeks of discontinuation of UT-15 and two within one month of discontinuation of UT-15 therapy. None of these subjects obviously required Flolan® at baseline and the need for Flolan® upon discontinuation of UT-15 suggests that the subject's status had deteriorated. The p-values for the pooled and individual studies when treating those subjects started on Flolan® within 1 month of discontinuing UT-15 as well as those who died or required transplant as worst outcomes, no longer are significant. For the pooled data, the p-value was 0.082. For the individual studies the p value was > 0.2.

A third analysis also included all those who were treated with Flolan® during the window of the study as worst outcomes. In addition, there was one subject whose status at the time of discontinuation appeared to be inconsistent with the imputed measurement from week 1. The value for this subject was excluded. The p-values for this analysis for the pooled data was >0.1. The p-values for each of the individual studies were >0.2.

The above analyses presume that all subjects who discontinued UT-15 therapy and received Flolan® did so because they deteriorated. Some or all of these subjects, however, may have been started on Flolan® because no other options were available. An alternate analysis, performed by the sponsor imposes a last rank value for all those who discontinued prematurely, even if the reason was death, deterioration or need for transplantation. This analysis removes one source of the bias against the placebo in that no subject received a worst outcome. This analysis is sponsor's analysis # 4 in this review. The p-value for the pooled studies was 0.011 and that for the individual studies was between 0.07-0.08.

In summary, the study did not succeed by the pre-specified criteria of success. Neither study P01:04 nor P01:05 was by itself statistically significant by a method of analysis that biases results towards UT-15 treatment. Additional analyses that corrected for the asymmetry in adverse events completely eliminate any benefit even for the pooled studies.

5.2 Supportive metrics

Since the primary outcome of the study did not succeed by the pre-specified criteria, supportive measures of efficacy are more difficult to interpret. Nevertheless, there is a suggestion from the supportive information that UT-15 may have some effect on symptoms associated with severe pulmonary hypertension. The supportive symptoms were collected only among those who completed the study. Those who discontinued for any reason did not have any values imputed. In addition, the supportive symptoms

were administered by the treating physician who might have been aware, based on the nature of infusion site reaction the subject's treatment.

Subjects showed improvement in the composite of sixteen signs and symptoms of pulmonary hypertension. The metric that was used was a composite of all these symptoms. Subjects were assigned a "+1" for symptoms present at baseline and absent after 12-weeks, and a "-1" for symptoms that went from absent to present. Symptoms that were present at baseline and present at end of study, or absent at baseline and absent at end of study were assigned a value of "0". The net change for each subject was averaged over all those who approximately 1 unit for those treated with UT-15. The specific symptoms that were improved or were less frequently worsened in the UT-15 group were dizziness, palpitations, orthopnea and chest pain. The most troublesome symptoms of pulmonary hypertension, dyspnea and fatigue did not appear to be differentially resolve across groups.

A second metric that was prospectively collected as a supportive end-point was the dyspnea fatigue index. This metric consists of three components with values ranging from 0-4. The three components are "magnitude of task", "magnitude of pace" and "functional impairment". The higher the value, the less symptomatic the subject. There was a net increase of approximately 1.4 units in the overall symptom score among those treated with UT-15, approximately equally divided among the three components of this metric.

The quality of life metric was the Minnesota Living With Heart Failure questionnaire. This questionnaire consists of 21 questions and is divided in to 4 dimensions. This questionnaire was validated among subjects with CHF but not among patients with pulmonary hypertension, although the specifics of the questionnaire should be broadly applicable to patients with pulmonary hypertension. The questionnaire consists of a global and three components termed dimensions (i.e. physical, economical and emotional dimension). This questionnaire was not apparently administered to all subjects. Overall the global QOL did not differ between the two treatments. The physical dimension [portion of the questionnaire, however, was statistically favored the UT-15 group.

Each subject was asked to rank his or her degree of breathlessness after each six-minute walk by the Borg-dyspnea scale. This metric ranged from 1-10. The higher numbers suggest greater degrees of shortness of breath. The exercise coordinator performed this task and consequently is more likely to have been shielded from telltale signs suggesting active drug or vehicle use. Both the pooled studies and each of the individual studies were highly significant in improvement ($p<0.01$) of this metric. The magnitude was approximately 0.8 units.

5.3 End points related to the natural course of the disease

Despite modest effects on measurements of performance and symptoms, there does not appear to be any evidence that UT-15 alters the natural course of pulmonary hypertension. Deaths, hospitalizations, cardiovascular/pulmonary hypertension hospitalizations or need for new or increases in medications were no different between groups. The need for inotropic or Flolan® support during the 12-week study did not differ between the two treatments.

There were a total of 19 subjects who died during the window of the study. Ten of these subjects were in the vehicle group and nine in the UT-15 group.

Hospitalizations were equivalent in both groups. There were 40 subjects who were hospitalized or had their hospitalizations prolonged among the vehicle group and 38 among the UT-15 group. Two of those hospitalized among those randomized to vehicle were hospitalized after accidentally receiving UT-15. The investigators at the various study sites did not adjudicate cause-specific hospitalizations. This reviewer, based on

the capsular summaries found 22 of those treated with UT-15 and 25 of those treated with vehicle had their hospitalizations prolonged or had a de novo hospitalization as a consequence of cardiovascular or pulmonary hypertension etiologies.

Subjects who status deteriorates may require new medications or increase in doses of ongoing medications. A difference in the need to alter medications may suggest a benefit of a given treatment. For the purposes of this assessment the following drug classes were considered: loop diuretics, calcium channel blockers, vasodilators (including hydralazine, clonidine, nitrates), ACE inhibitors or angiotensin II blockers, oxygen, Flolan®, pressors, steroids, digoxin, aldactone or non-loop diuretics. The number of subjects who required no change in medication or no increase in medication comparing baseline to week-12 were similar in both groups.

There was no difference in the number of subjects who required Flolan® or inotropic support. This reviewer counted 12 subjects in the UT-15 group and 10 in the vehicle group that required one of these medications.

5.4 Hemodynamics

Among those who completed the study, there was a modest improvement in catheterized hemodynamics. Right atrial pressures, pulmonary artery pressures (mean, systolic and diastolic) and pulmonary vascular resistance were decreased. Cardiac index, stroke index and mixed venous oxygenation were increased. The effects on hemodynamics, though statistically significant were in general small and of uncertain consequence. For cardiac index the net change (assuming that the data for those measured is consistent with the whole group) there was a net increase of 8%. There was an approximately 5% (3 mm Hg) decrease in mean pulmonary artery pressure. There was an approximately 18% decrease in pulmonary vascular resistance.

5.5 Dosing

Dosing was predicated on improving symptoms of pulmonary hypertension while minimizing excessive pharmacologic effect or infusion related adverse events. It is therefore not possible to define either the initial, optimal or an appropriate dose range of use for UT-15 based on the data from this study or from the database as a whole.

Despite nearly an order of magnitude increase in mean infusion rate, there was minimal increase in walking distance among those treated with UT-15. The observed differences more reflect a worsening of the distance walked by the vehicle group than by an improvement among those taking larger and larger infusions of UT-15. There was no randomized withdrawal to ascertain a persistent (or any) benefit of UT-15. In fact among the handful of subjects who discontinued UT-15 acutely, no evidence of rebound was described. It is therefore unclear if there was any persistent beneficial effect of UT-15.

5.6 Comparison with Flolan

Flolan is approved for the treatment of patients with primary pulmonary hypertension Class III and IV. However, its use is difficult and inconvenient. The infusion of Flolan requires the insertion of an indwelling central catheter with the attendant risks of the inserting the catheter and the subsequent risk of catheter infection. Flolan has a rapid half-life and rapid dissipation of its hemodynamic effects. Any inadvertent interruption of the infusion is potentially life threatening. Flolan is chemically labile at room temperatures and must be reconstituted every 8 hours or kept at cold temperatures during the infusion. UT-15 was developed to avoid these problems and thereby delay the time till Flolan treatment becomes infusion.

There is no scientific rationale to concurrently use UT-15 with Flolan. There is also no empirical safety or efficacy information on the concurrent use of these drugs. UT-15 is intended as treatment of pulmonary hypertension solely to postpone starting Flolan. There is no study that randomized patients to Flolan or UT-15 that demonstrates

equivalent outcomes so that there may be unintended negative consequences in the delay of Flolan infusion. Comparing the labeling of Flolan to the likely labeling of UT-15 the mortality benefit for Flolan does not appear to be uniformly observed with UT-15. The current labeling of Flolan states:

> *"Survival was improved in NYHA functional Class III and IV PPH patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period 8 of 40 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P=0.003)."*

In the pivotal UT-15 studies (P01:04 and P01:05) the drug demonstrated no mortality benefit. The UT-15 study population consisted of predominantly (55%) primary pulmonary hypertension patients with the vast majority NYHA Class III and this portion of the population coincides with the population for which Flolan demonstrated a mortality benefit. There were 9 deaths among those randomized to UT-15 and 10 deaths among those randomized to vehicle during the 12-week study. Five of the 9 deaths on UT-15 were patients with primary pulmonary hypertension while 8 of the 10 deaths on vehicle were patients with primary pulmonary hypertension.

Performance benefit on the 6-minute walk for UT-15 patients was small, approximately 3% of the baseline walk distance. Performance among those with Flolan was approximately 35-50% of baseline walk distance. Admittedly, the basis of comparison is across studies with different designs. Nevertheless, the magnitude of effects a does give one pause before assuming equivalence between UT-15 and Flolan.

6 Integrated review of safety

6.1 Methodology

6.1.1 Mortality

Mortality was a primary end point in no studies. Most studies were of duration short compared with the lifetime of patients with pulmonary hypertension, so most mortality occurred in the 12-week studies P01:04 and P01:05 and the long-term open-label follow-on study P01:06.

This review contains narrative summary of all of the deaths developed from the sponsor's summaries and the case report forms.

6.1.2 Withdrawals

Case report forms were available for medically related withdrawals. There were also narrative summaries of these events.

6.1.3 Adverse events

Case report forms provided a mechanism for reporting adverse events and identifying their seriousness, severity, and relationship to study drug. The sponsor provided a summary narrative and case report forms for serious nonfatal adverse events.

Common adverse events were separately tabulated for studies of normal volunteers, placebo-controlled studies in pulmonary hypertension, and chronic studies of open-label administration.

6.1.4 Laboratory findings

The principal laboratory data of interest were obtained during placebo-controlled studies. The sponsor tabulated changes from baseline in mean laboratory values. Electronic datasets provided by the sponsor were used to construct baseline-vs.-on-treatment plots for data from continuous measurements. Such graphs show the relationship between baseline and on-treatment values with a 45-degree line of no effect for orientation and, in the margins, box-and-whiskers plots of the distributions in various treatment groups.

6.1.5 Vital signs

Vital signs were monitored as a conventional aspect of in-hospital patient care, and they were systematically collected for the first 8 hours of randomized treatment in placebo-controlled studies P01:04 and P01:05.

6.1.6 ECGs

ECGs were collected at baseline and at the end of active treatment in the placebo-controlled studies. These were analyzed much like the laboratory data from these studies.

6.2 Results

6.2.1 Exposure

The sponsor's Integrated Summary of Safety covers the period up to 31 May 2000 for deaths and serious adverse events, and up to 4 February 2000 for other safety data.

A summary of studies, exposure to study drug, deaths, and serious adverse events is shown in Table 2.

Table 2. Exposure to UT-15[4].

Study	N	Route	Duration	On UT-15		
				Deaths	With	SAE
Studies of clinical pharmacology in subjects with CHF						
P76:01	12/12	iv	—	—	—	—
P01:01	14/14	iv	1.5 h	0	/4	12
P01:02	25/25	sc, iv	4 h	0	10/10	
Studies of pharmacokinetics in normal volunteers						
P01:07	15/15	sc, iv	2.5 h	0	0	0
P01:08	29/29	sc	2 x 6 h	0	0	0
P01:09	14/14	sc	28 d	0	/8	0
P01:10	6/6	sc	8 h	—	—	—
Controlled studies in pulmonary hypertension						
P01:03	26/17	sc	56 d	0	2/2	4
P01:04	224/113	sc	84 d	4	17/17	40
P01:05	246/123	sc	84 d	5	16/14	
Uncontrolled studies in pulmonary hypertension						
P01:06	631/631[5]	sc	>819 d	36	150	170
P01:11	3/3	sc	240 d	0	0	1
P01:12	16/16	sc	10 d	—	—	—
Portopulmonary hypertension						
P02:01	9/9	sc	2.5 h	0	—/0	—
Peripheral vascular disease						
P03:01	8/—	iv	—	—	—	—

A brief description of these studies is given in the following paragraphs.

Study P01:01 was a two-period crossover study in which subjects were titrated to the maximum tolerated dose of Flolan and UT-15 and maintained for 90 minutes.

Study P01:02 was a parallel study in which subjects received UT-15 10 ng/kg/min for 1.25 h, followed by 5, 10, or 20 ng/kg/min for 2.5 h.

Study P01:03 was a parallel study in which subjects received placebo or UT-15 for 8 weeks.

Studies P01:04 and P01:05 were parallel studies in which subjects received placebo or UT-15 for 12 weeks.

Study P01:06 is an ongoing open-label study conducted among subjects previously enrolled in Studies P01:03, P01:04, or P01:05, and 208 subjects newly enrolled. As of the cutoff date, exposure was 476 subject-years, with 224 subjects treated for more than 1 year.

Study P01:07 was a two-period crossover study of bioavailability, comparing intravenous and subcutaneous administration of UT-15 15 ng/kg/min over 2.5 hours.

Study P01:08 was a two-period cross-over study of pharmacokinetics, comparing placebo with acetaminophen 1000 mg in subjects on sc infusions of UT-15 15 ng/kg/min for 7 days.

Study P01:09 was an open-label, forced titration study in which normal subjects received ascending doses of UT-15 2.5, 5, 10, and 15 ng/kg/min each for 7 days.

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[4] *N=total enrollment / exposed to UT-15; With=withdrawals total/medical*

[5] *The study is ongoing. The numbers refer to the NDA cutoff date of 1 October 2000.*

Study P01:11 was an open-label study of the transition to UT-15 of subjects receiving Flolan.

Study P02:01 was an open-label, baseline-controlled study with dosing at 10 ng/kg/min sc for 2.5 h.

Study P76:01 was a single-center, open label study in subjects NYHA III-IV CHF.

6.2.2 Deaths

Two subjects died subsequent to completion of study P01:02.

- Study P01:02 subject #02005 was a 47 year old, 72-kg, Caucasian female with a 4-year history of primary pulmonary hypertension, NYHA IV at baseline. She completed study with UT-15 without problems except intermittent backache[6]. The following day, she had a central venous catheter placed for Flolan administration, but she developed electromechanical dissociation and died despite CPR efforts, prior to Flolan administration. The investigator and sponsor regard the death as not reasonably attributable to UT-15.
- Study P01:02 subject #04004[7] was a 39 year old female with NYHA III primary pulmonary hypertension who completed study with UT-15 without incident. She remained in hospital for insertion of a central venous catheter and was discharged on Flolan 4 ng/kg/min. She was readmitted the following day (2 days after the last dose of UT-15) with syncope and dizziness, seized, had a brady-asystolic arrest, and died the same day despite CPR efforts. Death was attributed to decompensated cor pulmonale. The investigator and sponsor regard the death as not reasonably attributable to UT-15.

In studies P01:04 and P01:05, there were 9 deaths (3.8%) on UT-15 and 10 deaths (4.3%) on placebo.

Deaths on UT-15 are summarized in the paragraphs below:

- Study P01:04 subject 004017 was a 32 year old, 70-kg female with a 1-month history of PPH, NYHA III at baseline. She was having injection site pain and inject site reaction throughout treatment. She developed right heart failure on day 21 (UT-15 4 ng/kg/min). She was hospitalized and died, 3 days after decreasing the dose of study drug. Events were attributed to underlying disease.
- Study P01:04 subject 009006 was a 29-year-old, 55-kg female with congenital atrial septal defect, NYHA III at baseline. She had a stroke (pontine infarct with bilateral loss of vision) on day 2, several hours after Swan-Ganz removal. She received UT-15 1 ng/kg/min for about 9 hours. Thrombotic stroke was diagnosed by MRI and cerebral angiography, and she was treated with thrombolysis, but died 3 days after study drug administration. Events were attributed to catheterization and not to study drug.
- Study P01:04 subject 010002 was a 40-year-old, 114-kg female with mixed connective tissue disease, NYHA IV at baseline. She was hospitalized on day 57 of treatment (UT-15 7.5 ng/kg/min) with right

[6] *CRF is ambiguous as to whether this subject discontinued for backache.*

[7] *CRF was not provided.*

heart failure, and treated with diuretics, inotropes, and increased UT-15 (12 ng/kg/min). On day 81 (apparently still on UT-15), she developed ventricular tachycardia that did not respond to resuscitation.

- Study P01:04 subject 023002 was a 15-year-old 40-kg female status post repair of ventricular septal defect, NYHA II at baseline. On day 52 of treatment with UT-15 4 ng/kg/min, she had respiratory arrest at home and died in the ER despite resuscitation attempts. Death was attributed to her underlying condition.
- Study P01:05 subject 004503 was a 36 year old, 49-kg Hispanic female with a 3-year history of primary pulmonary hypertension, NYHA III at baseline. She discontinued UT-15 5 ng/kg/min on day 49 to undergo medical termination of pregnancy. Her hospital course was complicated by low cardiac output, disseminated intravascular coagulopathy, oliguria, hypoxemia, and sepsis. She died 7 days after discontinuing UT-15. Death was attributed to sepsis.
- Study P01:05 subject 051007 was a 28 year old 58-kg Caucasian female with recent onset of primary pulmonary hypertension, NYHA II at baseline. At her week-12 cardiac catheterization (day 86 on UT-15 20 ng/kg/min), she had vasovagal syncope, followed by complete A-V block, electromechanical dissociation, and death.
- Study P01:05 subject 054005 was a 20 year old 40-kg Caucasian female with congenital left-to-right shunt, NYHA III at baseline. She was hospitalized on day 43 of treatment (UT-15 2.5 ng/kg/min) for worsening hemodynamics and hypoxemia, thought to be pulmonary embolus. She was treated with vasodilators and anticoagulation, but died 8 days after admission. It is unclear how long previously UT-15 was stopped. Death was attributed to pulmonary embolus and underlying condition and not to study drug.
- Study P01:05 subject 055005 was a 32 year old 87-kg female with a 9-month history of primary pulmonary hypertension, NYHA IV at baseline. She was receiving UT-15 1.25 ng/kg/min up to day 6, when she was hospitalized with recurrent syncope, chest pain, and hypotension. Myocardial infarction was suspected, but she developed intractable ventricular fibrillation prior to angiography. The investigator and sponsor disagree on the possible role of UT-15 in these events.
- Study P01:05 subject 058001 was a 39 year old, 83-kg Caucasian male with a 15-month history of primary pulmonary hypertension, NYHA III at baseline. He was receiving UT-15 1.5 ng/kg/min on day 17 when he was admitted to hospital for hemoptysis, hyponatremia, and hyperkalemia. Pulmonary embolus was suspected. Renal and respiratory function declined and he died on day 7 of admission (unclear whether still on UT-15) with bradycardia followed by cardiac arrest. These events were not attributed to UT-15.

Deaths on placebo are summarized in the paragraphs below.

- Study P01:04 subject 009012 was a 56 year old 80-kg Caucasian male with a 2-year history of primary pulmonary hypertension, NYHA IV at baseline. He died on day 9, one day after being admitted to

hospital for right heart failure. Events not considered related to study drug.

- Study P01:04 subject 010001 was a 65 year old 80-kg male with a 1-year history of mixed connective tissue disease, NYHA IV at baseline. On day 36, he was hospitalized with hematemesis and acute respiratory distress. Six days later, he developed bradycardia and cardiac arrest from which he could not be resuscitated. Events not considered related to study drug.
- Study P01:04 subject 015003 was a 23 year old 60-kg Caucasian female with a 3-year history of systemic lupus erythemetosis and mixed connective tissue disease, NYHA III at baseline. She was hospitalized on day 46 for dyspnea and hypoxemia attributed to right-to-left shunting through a patent foramen ovale. She arrested during a pericardiocentesis procedure and did not survive. Events were not attributed to study drug.
- Study P01:04 subject 016003 was a 67 year old 54-kg female with a 4-month history of scleroderma, NYHA III at baseline. She was hospitalized on day 85 for acute respiratory failure. Death 3 days later was attributed to progression of right heart failure.
- Study P01:04 subject 016006 was a 57 year old 45-kg female with a 5-year history of primary pulmonary hypertension, NYHA III at baseline. On day 74, she was hospitalized with a 3-day history of progressive right heart failure symptoms. She underwent 'week-12' right heart catheterization and the decision was made to start IV Flolan, but a few hours later she arrested and could not be resuscitated. Death was attributed to progression of right heart failure.
- Study P01:05 subject 052006 was a 46 year old 97-kg female with a 1-year history of primary pulmonary hypertension, NYHA III at baseline. On day 32, she was hospitalized with upper respiratory infection, fever, and heart failure symptoms. The blind was broken and study drug was discontinued. She died from cardiogenic shock the following day.
- Study P01:05 subject 060006 was a 17 year old 55-kg Caucasian female with an 11-year history of primary pulmonary hypertension, NYHA IV at baseline. On day 60, she was hospitalized with right heart failure. She died 2 days later following cardiac arrest.
- Study P01:05 subject 060015 was a 19 year old 60-kg Caucasian female with a 4-year history of primary pulmonary hypertension, NYHA III at baseline. On day 47, she was hospitalized for right heart failure. Despite treatment, she progressed to cardiogenic shock and died the following day.
- Study P01:05 subject 065004 was a 51 year old 64-kg Caucasian female with a 6-month history of primary pulmonary hypertension, NYHA III at baseline. On day 18, she was hospitalized for dyspnea and chest pain, and had a cardiac arrest from which she could not be resuscitated.
- Study P01:05 subject 065011 was a 59 year old 67-kg Caucasian male with a 1-year history of primary pulmonary hypertension, NYHA

III at baseline. On day 43, he was hospitalized for hypoxemia and was switched to Flolan. Thirty-one days later, he died suddenly. Autopsy revealed features of PPH and heart failure; death was attributed to arrhythmia.

The following deaths were reported with open-label follow-on study P01:06. None were considered reasonably attributable to study drug.

- P01:06 subject 302003 was a 44 year old Caucasian female, 75 kg, with a 3-year history of primary pulmonary hypertension, NYHA III at baseline. After 20 months on UT-15 (apparently at 37.5 ng/kg/min), she was hospitalized and died from a pulmonary hypertensive crisis.
- Study P01:06 subject 302013 was a 13 year old Caucasian female with a 3 month history of primary pulmonary hypertension, NYHA III at baseline. She died from pulmonary hemorrhage after 1 year on UT-15, most recently 18 ng/kg/min.
- Study P01:06 subject 402007 was a 58 year old 76 kg Caucasian female with a 2 year history of primary pulmonary hypertension, NYHA III at baseline. She died from hypotension after 1 year on UT-15, most recently 25 ng/kg/min.
- Study P01:06 subject 603604[8] was a 49 year old Caucasian male with a 4 month history of pulmonary hypertension associated with scleroderma, NYHA III at baseline. He was discharged from hospital on the day following initiation of UT-15, and then was readmitted on day 2 to day 5, and then again on day 6 to day 13. On day 14, he was found unresponsive at home and died the same day in the hospital ER, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 404013 was a 67 year old Caucasian female, 59 kg, with a 2 year history of pulmonary hypertension associated with scleroderma, NYHA IV at baseline. She died of heart failure at 6 months, attributed to underlying disease, while receiving UT-15 24 ng/kg/min.
- Study P01:06 subject 409002 was a 61 year old Caucasian female, 45 kg, with a 2 year history of pulmonary hypertension associated with mixed connective tissue disease, NYHA III at baseline. She died at 6 months from sepsis, while receiving UT-15 31 ng/kg/min.
- Study P01:06 subject 409007 was a 36 year old Caucasian female, 95 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She completed a previous trial on active treatment. She died from cardiac arrest on day 5, while receiving UT-15 14 ng/kg/min.
- Study P01:06 subject 409019 was a 35 year old Caucasian male with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. He died a sudden death at month 3, while receiving UT-15 18 ng/kg/min.
- Study P01:06 subject 410005 was a 28 year old Caucasian female with a 6 month history of pulmonary hypertension associated with mixed connective tissue disease, NYHA III at baseline. She died of

[8] *Adverse event pages of CRF are missing for this subject. Apparently, he was newly enrolled in Study P01:06.*

worsening pulmonary hypertension after 13 months, while receiving UT-15 3 ng/kg/min.

- Study P01:06 subject 410022 was a 35 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She died at 6 months, attributed to pulmonary hypertension and right heart failure, while receiving UT-15 6.5 ng/kg/min.
- Study P01:06 subject 410026 was a 32 year old Black female, 72 kg, with a 3 month history of primary pulmonary hypertension, NYHA III at baseline. She died at 5 months with pulmonary hypertension, while receiving UT-15 1.7 ng/kg/min.
- Study P01:06 subject 412005 was a 49 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She died a sudden death at 3 months, while receiving UT-15 19 ng/kg/min.
- Study P01:06 subject 414002 was a 46 year old Caucasian female, 103 kg, with a 2 year history of primary pulmonary hypertension, NYHA III at baseline. She had a sudden death at 2 months, while receiving UT-15 11 ng/kg/min.
- Study P01:06 subject 414011 was a 28 year old Caucasian female with a 7 month history of pulmonary hypertension associated with systemic lupus erythematosus, NYHA II at baseline. She received placebo during the previous study. She died on day 21 of cardiac arrest associated with progressive right heart failure, while receiving UT-15 2 ng/kg/min.
- Study P01:06 subject 420010 was a 19 year old Hispanic female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She received placebo during the previous study. She had sudden death at 3 months, while receiving UT-15 23 ng/kg/min.
- Study P01:06 subject 624603 was a 20 year old Hispanic female, 57 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She was newly recruited into this study, so there was no previous exposure to UT-15. She died on day 34, from cardiac arrest associated with severe pulmonary hypertension, while receiving an unknown dose of UT-15.
- Study P01:06 subject 550014 was a 51 year old Caucasian male, 81 kg, with a 4 year history of primary pulmonary hypertension, NYHA IV at baseline. He died at day 17 from low cardiac output, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 550023 was a 38 year old Caucasian female with a 1 year history of pulmonary hypertension associated with mixed connective tissue disease, NYHA IV at baseline. She died on day 42 with progressive pulmonary hypertension, while receiving UT-15 9 ng/kg/min.
- Study P01:06 subject 552004 was a 27 year old Caucasian female, 59 kg, with a 5 month history of primary pulmonary hypertension, NYHA III at baseline. She died at 3 months from cardiac arrest and

right heart failure, while receiving UT-15 10 ng/kg/min.

- Study P01:06 subject 553011 was a 12 year old Caucasian female with pulmonary hypertension associated with a congenital left-to-right shunt, NYHA III at baseline. She received UT-15 in a previous study. She died from pneumonia and ARDS on day 9. The CRF in conflicted about whether she was receiving UT-15 (13 ng/kg/min) up to the time of death.
- Study P01:06 subject 554004 was a 20 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She had a sudden death at 4 months, while receiving UT-15 10 ng/kg/min.
- Study P01:06 subject 657601 was an 83 year old Caucasian male with a 5 year history of primary pulmonary hypertension, NYHA III at baseline. He had a sudden death at 2 months, while receiving UT-15 3.7 ng/kg/min.
- Study P01:06 subject 559008 was a 35 year old Caucasian male, 68 kg, with a 7 year history of primary pulmonary hypertension, NYHA III at baseline. He previously received placebo. He died on day 7 with progressive right heart failure, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 560002 was a 38 year old Caucasian female, 50 kg, with a 3 year history of primary pulmonary hypertension, NYHA III at baseline. She died from decompensated right heart failure at 4 months, while receiving UT-15 13 ng/kg/min.
- Study P01:06 subject 560014 was a 56 year old Caucasian female, 60 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She died from right heart failure at 4 months, while receiving UT-15 7 ng/kg/min.
- Study P01:06 subject 565014 was a 57 year old Caucasian female, with a 4 month history of pulmonary hypertension associated with scleroderma, NYHA III at baseline. She died on day 47 with progressive right heart failure, while receiving UT-15 5 ng/kg/min.
- Study P01:04 subject 04018 was a 65 year old Caucasian female, 54 kg, with primary pulmonary hypertension, NYHA III at baseline. She died of right heart failure on day 196 while receiving UT-15 28 ng/kg/min.
- Study P01:04 subject 05010 was a 61 year old Caucasian female, 82 kg, with lupus, NYHA IV at baseline. She died with right heart failure on day 315 while receiving UT-15 6 ng/kg/min.
- Study P01:04 subject 20005 was a 21 year old Hispanic female, 53 kg, with primary pulmonary hypertension, NYHA II at baseline. She died on day 294 with sepsis and pneumonia, while receiving 38 ng/kg/min.
- Study P01:05 subject 22501 was a 64 year old Caucasian female, 50 kg, with systemic sclerosis, NYHA III at baseline. She died with acute exacerbation of respiratory failure, on day 290, while receiving UT-15 23 ng/kg/min.
- Study P01:05 subject 53003 was a 61 year old Caucasian female, 74

kg, with primary pulmonary hypertension, NYHA IV at baseline. She died, with progressive right heart failure, on day 530, while receiving UT-15 46 ng/kg/min.

- Study P01:05 subject 53009 was a 56 year old Caucasian female, 64 kg, with primary pulmonary hypertension, NYHA III at baseline. She died on day 265 with sepsis, renal failure, and pneumonia, while receiving UT-15 17 ng/kg/min.
- Study P01:05 subject 64005 was a 54 year old Caucasian female, 61 kg, with primary pulmonary hypertension, NYHA III at baseline. She had a sudden death attributed to cor pulmonale on day 162, while receiving UT-15 19 ng/kg/min.
- Study P01:06 subject 14601 was a 73 year old Caucasian female, 65 kg, with primary pulmonary hypertension, NYHA IV at baseline. She died a sudden death on day 115, about 6 weeks after a myocardial infarction, while receiving UT-15 18 ng/kg/min.
- Study P01:06 subject 51601 was a 53 year old Caucasian female, 74 kg, with primary pulmonary hypertension, NYHA III at baseline. She died with pulmonary edema on day 147, while receiving UT-15 21 ng/kg/min.
- Study P01:06 subject 59603 was a 33 year old Caucasian female, 50 kg, with primary pulmonary hypertension, NYHA III at baseline. She died with right heart failure on day 37, while receiving UT-15 8 ng/kg/min.

A total of 116 subjects discontinued UT-15 in studies P01:04, P01:05 and (to the original cutoff date for) P01:06. In 40% of these the dose of UT-15 was apparently terminated abruptly. Half of the subjects who terminated UT-15 went on to receive Flolan. There were 15 deaths in the first 30 days after termination of UT-15 in study P01:06, 9 among subjects discontinued for deterioration. Five deaths occurred in the first 24 hours after discontinuing UT-15.

- Study P01:05 subject 550013 was a 34 year old Indian female with primary pulmonary hypertension, NYHA III at baseline. She discontinued from UT-15 2 ng/kg/min at 6 weeks because of infusion site pain. Other complaints were increased breathlessness and fatigue. The following day, she died a sudden death, attributed to progressive pulmonary hypertension.
- Study P01:06 subject 409001 was a 30 year old Caucasian female with primary pulmonary hypertension, NYHA II at baseline. She discontinued at 4 months (17 ng/kg/min) for pain. Her death in the emergency room, 12 hours later, was attributed to severe right heart failure.
- Study P01:03 subject 02010 was a female with primary pulmonary hypertension, NYHA III at baseline. After 3 months on UT-15, finally at 18 ng/kg/min, she developed sepsis and worsening pulmonary hypertension and she was discontinued to initiate Flolan. Death 2 days later was attributed to sepsis.
- Study P01:05 subject 58009 was a 39 year old female, 55 kg, with congenital left to right shunt, NYHA III at baseline. After 170 days on UT-15, up to 6 ng/kg/min, she was hospitalized with syncope and

aspiration pneumonia. Five weeks later, UT-15 was discontinued and Flolan was started, but she developed sepsis and complete A-V block and died the following day.

- Study P01:06 subject 61609 was a 31 year old female, 57 kg, with primary pulmonary hypertension, NYHA IV at baseline. She developed severe dyspnea and hypoxia on day 10, discontinued UT-15 5 ng/kg/min and started Flolan. She died the following day with hypoxia.

The other ten deaths occurred 2, 3, 3, 6, 8, 8, 9, 10, 13, and 17 days after discontinuation of UT-15.

6.2.3 Withdrawals

Essentially all of the withdrawals were medically related. The most common reason for withdrawal among normal volunteers was injection site pain and injection site reaction. Among subjects with pulmonary arterial hypertension of various etiologies, the most common reasons for withdrawals were plausibly related to disease progression.

6.2.4 Adverse events

6.2.4.1 Serious

There was one serious adverse event in study P01:01 with no plausible relationship to UT-15.

- Study P01:01 subject 03001 discontinued during screening because of vasovagal reaction. This event took place before exposure to study drug.

There one serious adverse event in study P01:02 with no plausible relationship to UT-15.

- Study P01:02 subject #09002 developed respiratory distress subsequent to a hematoma of the neck during cardiac catheterization prior to study drug administration. Subject went on to receive protocol-specified exposure to UT-15 without incident.

There was one serious adverse event among 3 subjects in study P01:11 (transition from Flolan to UT-15).

- Study P01:11 subject 1102001[9] was a male of unknown age or history enrolled to switch from Flolan to UT-15 because of recurrent cerebral emboli. During the transition, he had a cerebral vascular accident that was attributed to the Flolan catheter.

Eight subjects are described as having had overdoses of UT-15 during studies P01:04 and P01:05 or follow-on study P01:06. The highest reported dose was a 1.5 mg bolus. Symptoms were headache, nausea, vomiting, and diarrhea. Some of these cases were dispensation errors among subjects randomized to placebo. Others were errors flushing the catheter or programming the infusion pump.

There were two cases of hemolytic anemia among subjects receiving UT-15 in studies P01:04 and P01:05. Both cases resolved during continued exposure to a lower dose of UT-15. A cause was not identified in either case.

6.2.4.2 Common

6.2.4.2.1 Normal volunteers

[9] *CRF not provided.*

Common adverse events among normal volunteers in acute studies are listed in Table 3.

Table 3. Common adverse events in acute studies with normal volunteers (Studies P01:07 and P01:08).

	Incidence (%) N=44		Incidence (%) N=44
Headache	59	Infusion site pain	14
Nausea	32	Pain	11
Vomiting	16	Jaw pain	11
Dizziness	16	Vasodilation	11

Headache, nausea, and dizziness were more common with iv dosing than with sc dosing.

Thirteen of 14 normal volunteers in 28-day study P01:09 reported adverse events, the most common of which are listed in Table 4.

Table 4. Common adverse events with chronic dosing among normal volunteers (study P01:09).

	Incidence (%) N=14		Incidence (%) N=14
Infusion site pain	86	Pain	43
Infusion site reaction	86	Infusion site bleed	36
Headache	79	Myalgia	29
Nausea	50	Akathesia[10]	21
Dizziness	43	Arthralgia	21

Infusion site pain and reaction were reported on low-dose UT-15, i.e., early in the study. No other events appeared to be related to dose.

6.2.4.2.2 Subjects with pulmonary hypertension

Eighty-three percent of subjects in acute studies of UT-15[11] reported at least one adverse event. The most common events are listed in Table 5.

Table 5. Common adverse events in acute studies of PAH (studies P01:01, P01:02, and P02:01).

	Incidence (%) N=48		Incidence (%) N=48
Headache	48	Jaw pain	10
Flushing	42	Vasodilation	8
Nausea	27	Vomiting	8
Back pain	17	Chest pain	8

None of the events appeared to be related to the dose of UT-15.

Common adverse events during longer-term exposure to UT-15 are shown in Table 6.

[10] *Restlessness (literally, cannot sit still).*

[11] *Studies P01:01, P01:02, and P02:01.*

Table 6. Common adverse events in chronic studies of PAH (studies P01:03, P01:04, P01:05, and P01:06)[12].

	Incidence (%) N=481		Incidence (%) N=481
Infusion site pain	83	Jaw pain	16
Infusion site reaction	81	Pain	15
Infusion site bleed	29	Dizziness	12
Diarrhea	27	Rash	11
Headache	25	Pharyngitis	11
Nausea	22	Vasodilation	11

Injection site pain and reaction were the most common causes of reductions in the dose of UT-15.

Common adverse events during the placebo-controlled studies (P01:04 and P01:05) are listed in Table 7.

Table 7. Incidence of adverse events in placebo-controlled studies of PAH (studies P01:04 and P01:05)[13].

	Placebo N=233	UT-15 N=236		Placebo N=233	UT-15 N=236
Infusion site pain	27	91	Edema	3	9
Infusion site reaction	27	90	Anorexia	2	6
Headache	25	33	Epistaxis	2	5
Diarrhea	16	29	Nausea and vomiting	<1	3
Nausea	18	26	Hypokalemia	—	2
Jaw pain	5	16	Melena	—	2
Vasodilation	5	14			

None of these events was evidently related to the dose of UT-15.

During open-label Study P01:06, 95% of subjects reported at least one adverse event and 27% had at least one reported serious adverse event, but only 4% had events considered possibly or reasonably attributable to study drug. The most common adverse events in P01:06, without regard to attribution, are shown in Table 8.

Table 8. Incidence (%) of common adverse events (P01:06)

	Incid		Incid
Any	95%	Headache	21
Infusion site pain	83	Jaw pain	16
Infusion site reaction	76	Pain	15
Diarrhea	29	Pharyngitis	12
Infusion site bleed/bruise	26	Dizziness	11
Nausea	23	Rash	11

Treatment-emergent serious adverse events with an incidence of at least 1% in the open-label study and without consideration of attribution were heart failure (5%), syncope (2%), pneumonia (2%), pulmonary hypertension (2%), and hypoxia (1%).

[12] *The table lists events without consideration of attribution. Most events were attributed to study drug.*

[13] *The table lists events without regard to attribution. Only events more common on UT-15 are shown.*

6.2.5 Adverse events of special concern

6.2.5.1 Hemorrhage

In controlled studies (P01:03, P01:04, and P01:05), 242 subjects on placebo experienced 162 hemorrhagic adverse events (0.67 per subject) and 253 subjects on UT-15 experienced 140 hemorrhagic events (0.55 per subject). The most common sites were the infusion site, ecchymosis, and epistaxis, only the latter of which was more common on UT-15 (12 vs. 4 events).

6.2.5.2 Infusion site pain/reaction

The most common and most clearly treatment-related adverse events were infusion site pain and infusion site reaction. There was no apparent relationship between infusion site pain or reaction and dose of UT-15.

During open-label administration in Study P01:06, 91% of subjects were on concomitant medications, the most common of which were analgesics, including local anesthetics (19%), topical pain medications (25%), opioids (35%), and other analgesics (45%).

6.2.6 Dose escalation

The dose of study drug rose progressively with time on open-label UT-15, as shown in Figure 4.

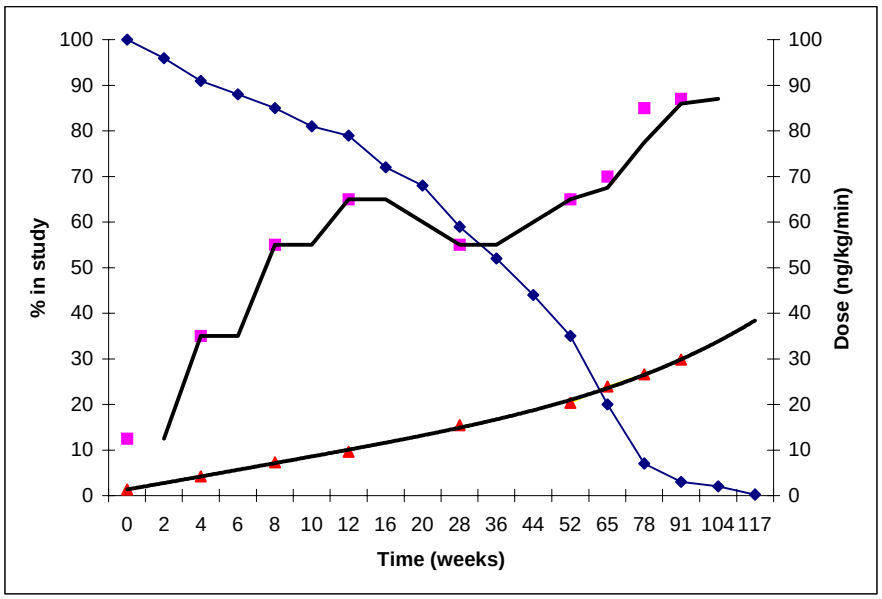

Figure 4. Proportion of subjects in study and UT-15 dosing (study P01:06).

Percentage of subjects followed in Study P01:06 as a function of time (diamonds; data from sponsor's 120-day safety update Table 12.1.1A) and the mean (triangles) and maximum (squares) dose of UT-15 in the same study (triangles; data from sponsor's 120-day safety update Table 12.1.1B).

Note that Figure 4 does not describe attrition during study P01:06. This study is ongoing. As of the cutoff date of 1 October 2000, 631 subjects had been enrolled, of whom 445 (71%) remained on study drug, 36 (6% had died, 136 (22%) had discontinued because of adverse events or need for rescue therapy, and 14 subjects had left for other reasons[14].

[14] *Four transplants, 7 withdrawals of consent, and 3 lost to follow-up (all of whom were known to be alive at some later date).*

The sponsor's analyses of dose escalation during study P01:06 demonstrate similar escalation among subjects originally randomized to placebo and UT-15.

Progressive dose escalation was also seen in studies P01:04-5, as shown in Table 9[15] .

Table 9. Dose escalation (studies P01:04 and P01:05).

	Placebo	UT-15
Baseline	1.2	1.2
Week 1	2.3	2.0
Week 6	10.0	5.9
Week 12	19.1	9.3

There is a much weaker case for tolerance in the studies supporting the approval of Flolan. There, doses trended upwards by less than a factor of two on average.

6.2.7 Laboratory findings

Mean changes in selected laboratory parameters are shown in Table 10. There were no significant shifts for these parameters, or for other hematological and urinalysis parameters.

Table 10. Baseline to on-treatment changes in mean laboratory parameters (Studies P01:04, P01:05)[16]

	Placebo			UT-15			Δ[2]
	BL	OT	Δ	BL	OT	Δ	
Chemistry							
Albumin	39.7	39.3	-0.4	40.0	39.7	-0.3	0.1
Alk phos	89	92	3	97	95	-2	-4
Bicarbonate	22	23	<1	23	23	<1	<1
Bilirubin (tot)	17	19	2	17	15	-2	-4
BUN	5.9	6.5	0.5	6.0	5.8	-0.2	-0.7
Calcium	2.2	2.2	<0.1	2.3	2.2	<0.1	<0.1
Chloride	104	103	<1	104	104	<1	<1
Creatinine	80	82	1	76	75	-2	-3
LDH	246	252	6	246	227	-19	-24
Potassium	4.2	4.1	<0.1	4.1	4.1	<0.1	<0.1
SGPT	29	27	-3	25	23	-2	<1
SGOT	31	30	-1	28	27	-1	<1
Sodium	140	139	<1	140	139	<1	<1
Hematology							
Hematocrit	0.46	0.46	<0.01	0.47	0.45	-0.02	-0.02
Hemoglobin	151	152	<1	153	148	-4	-5
Platelets	207	209	2	208	220	12	10
RBC	5.1	5.2	<0.1	5.4	5.3	-0.1	-0.2
WBC	7.3	7.8	0.5	7.3	7.2	-0.1	-0.6

[15] Sponsor's analysis of doses in studies P01:04 and P01:05 together; includes subjects who remained on study but off study drug, so it underestimates the actual doses in use.

[16] Table derived from query "lab del2": "SELECT [lab blot del act].TESTNAME, [lab blot del pcbo].MBL AS PBL, [lab blot del pcbo].MOT AS POT, [lab blot del pcbo].DEL AS PDEL, [lab blot del act].MBL AS ABL, [lab blot del act].MOT AS AOT, [lab blot del act].DEL AS ADEL, [ADEL]-[PDEL] AS DEL2 FROM [lab blot del act] INNER JOIN [lab blot del pcbo] ON [lab blot del act].TESTNAME = [lab blot del pcbo].TESTNAME;". Column headings are BL=baseline, OT=on-treatment, D=on-treatment minus baseline, D2=double difference from baseline and placebo.

Comparisons of baseline and on-treatment values for individual subjects' selected lab tests are shown in Figure 5 to Figure 8.

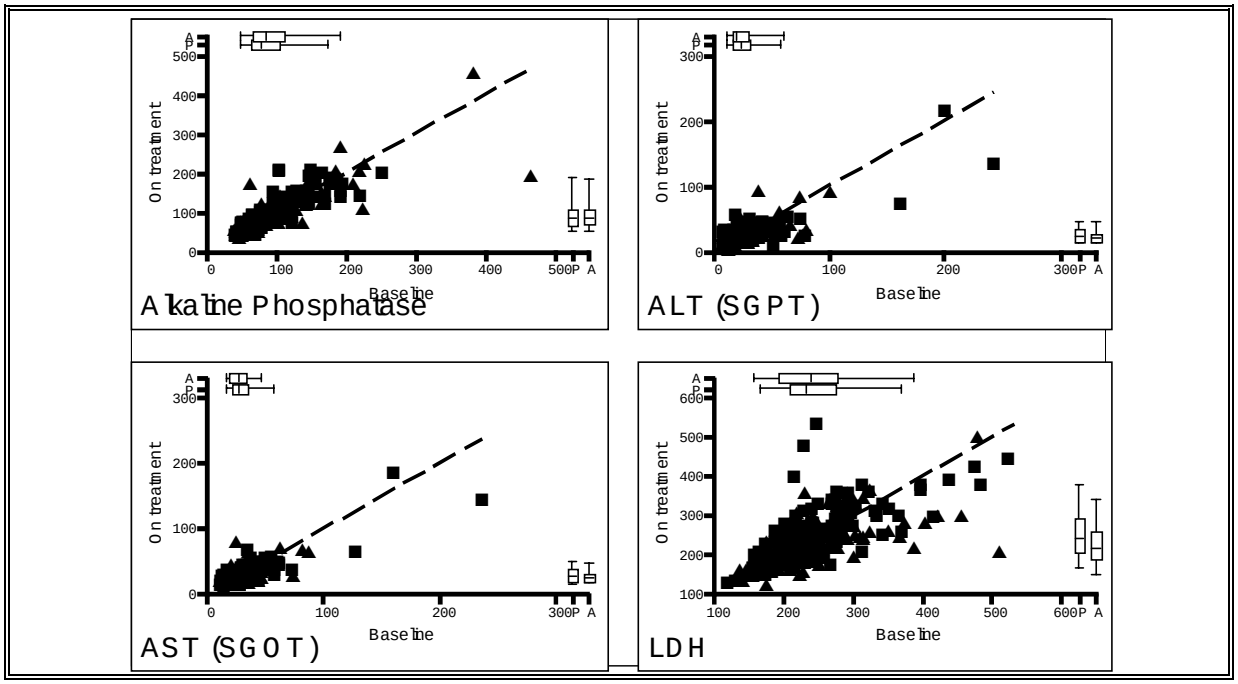

Figure 5. Baseline vs. on-treatment values of alkaline phosphatase, SGPT, SGOT, and LDH (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

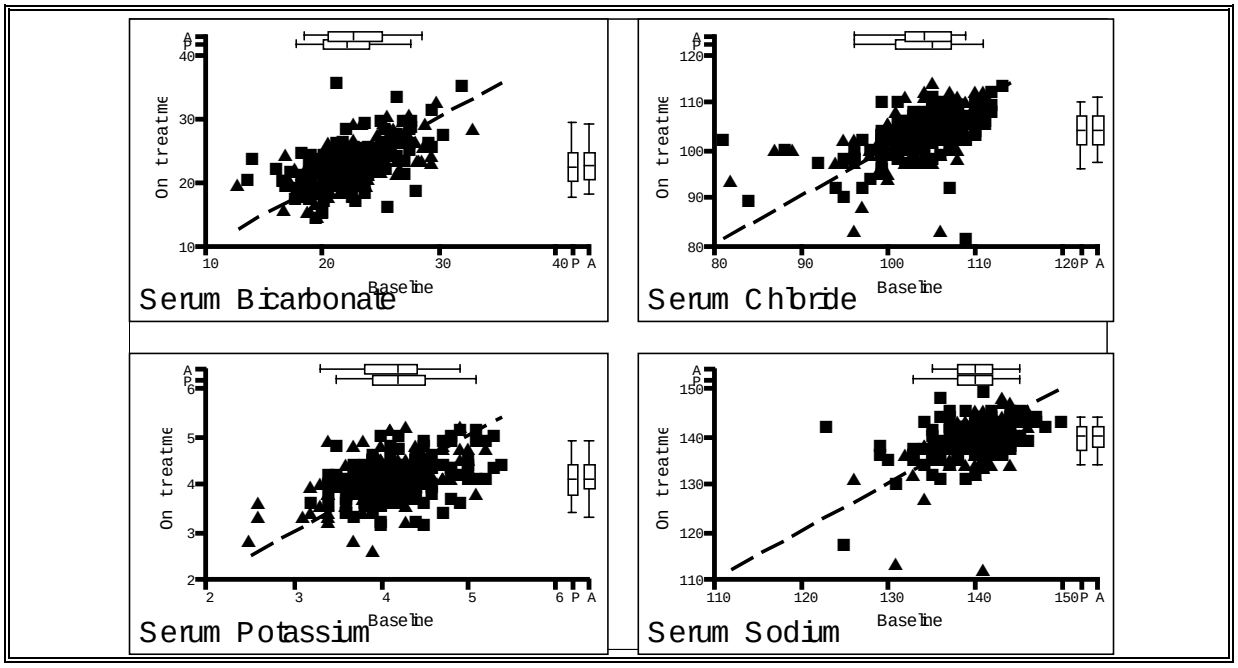

Figure 6. Baseline vs. on-treatment values of serum bicarbonate, chloride, potassium, and sodium (studies P01:04 and P01:05).

Analysis by reviewer. Data from stusdies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

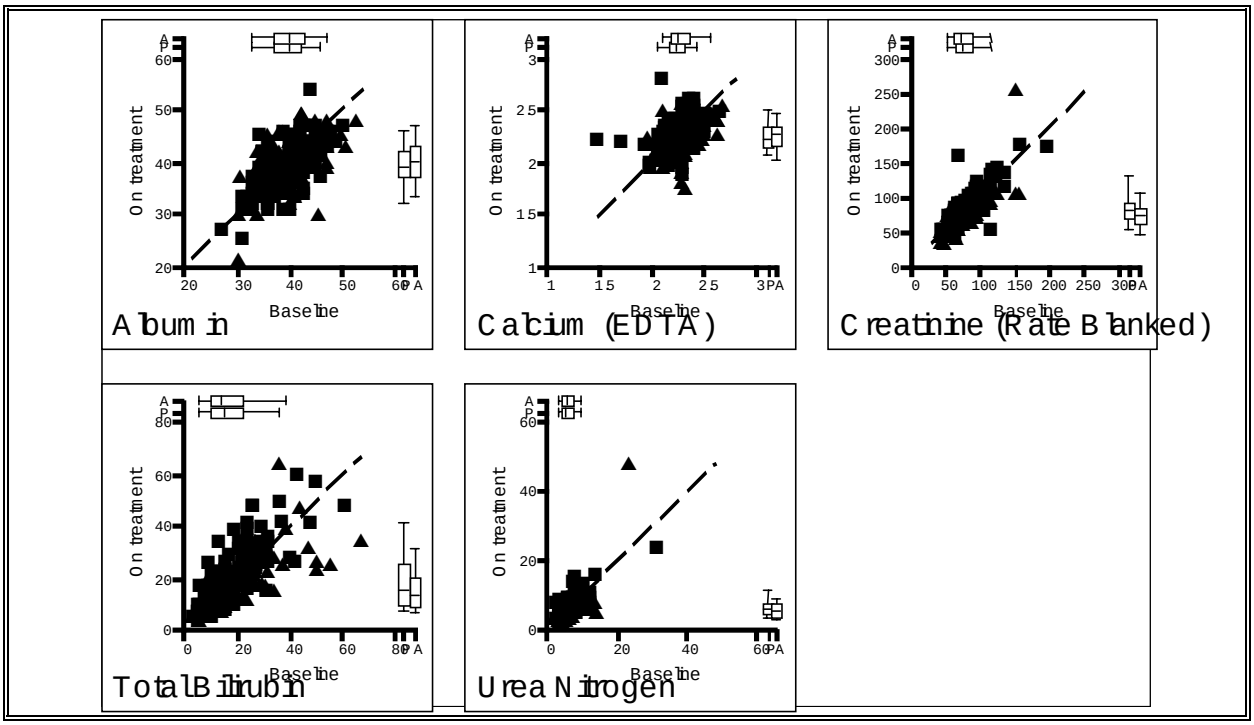

Figure 7. Baseline vs. on-treatment values of serum albumin, calcium, creatinine, bilirubin, and BUN (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

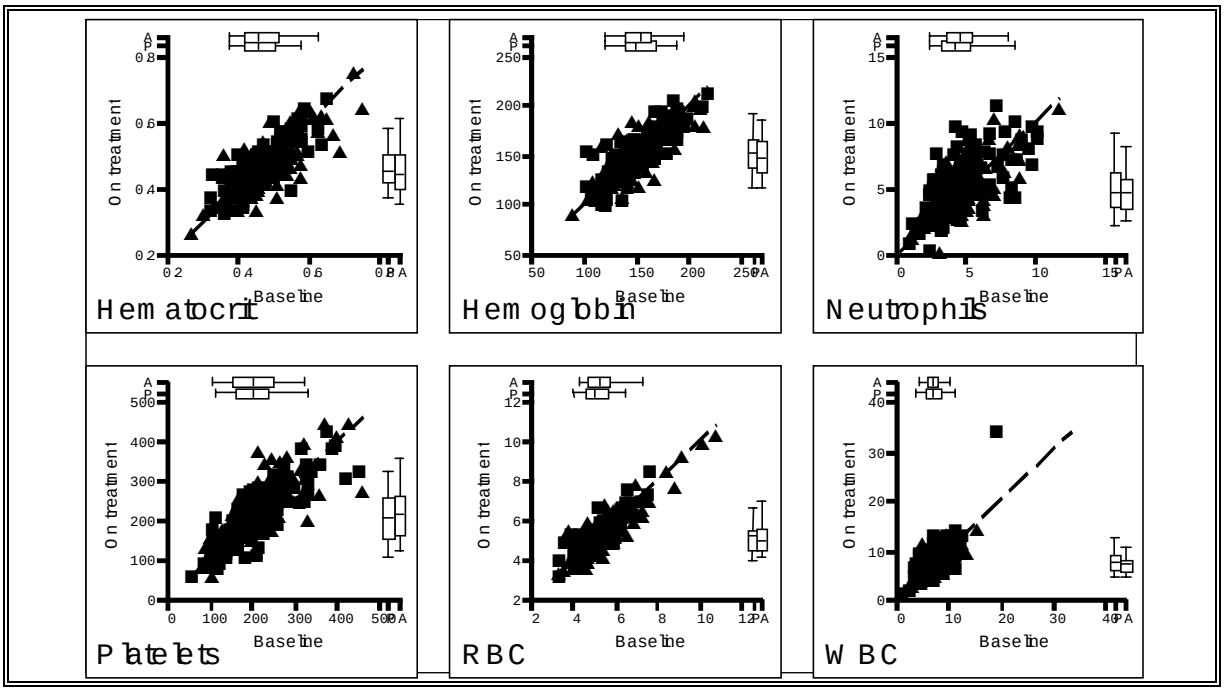

Figure 8. Baseline vs. on-treatment values of serum albumin, calcium, creatinine, bilirubin, and BUN (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

Of these laboratory assessments, there is an apparent trend to a reduction in potassium on treatment, but the shift does not appear to be related to treatment group.

6.2.8 Vital signs

Vital signs were assessed at intervals follow the first dose of randomized study drug. Changes in vital signs from baseline to 8 hours are shown in Table 11.

Table 11. Changes from baseline to 8 hours in vital signs (Studies P01:04, P01:05).

	Placebo	Active	Difference
SBP (mmHg)	-3.7	-1.9	1.8
DBP (mmHg)	-2.9	-2.8	0.1
HR (bpm)	-2.2	-3.5	-1.3

Despite the monitoring being generally in the afternoon to evening, these data show remarkably little placebo effect or nighttime decline. There is no significant effect of treatment on vital signs.

6.2.9 ECGs

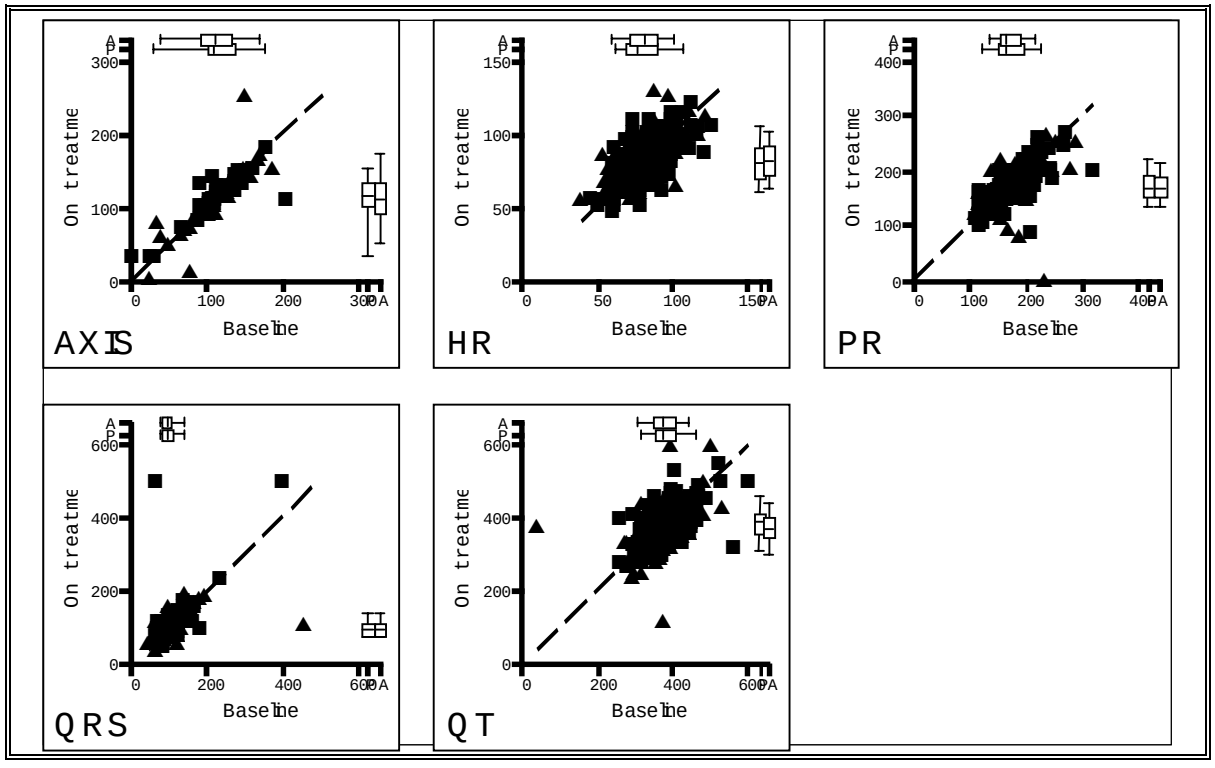

Figure 9. Baseline vs. on-treatment values for ECG parameters (Studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

Because of safety implications of outliers in QT or QTc, the numbers of subjects on placebo or active treatment were counted according to whether baseline and on-treatment QT or QTc were <450 ms. This analysis is shown in Table 12.

Table 12. Counts of subjects according to shifts in QT or QTc (Studies P01:04, P01:05)[17].

		QT				QTc			
		Placebo N=209		UT-15 N=194		Placebo N=209		UT-15 N=194	
		On-treatment value							
		<450	≥450	<450	≥450	<450	≥450	<450	≥450
Base-line	<450	184	9	186	3	109	35	104	27
	≥450	7	9	3	2	26	39	28	35

The analysis does not suggest that subjects on active treatment were more likely than subjects on placebo to have significant increases in QT or QTc.

6.3 Summary

Exposure was about 250 subjects or 50 subject-years in controlled studies and 631 subjects or 476 subject-years in long-term open-label use. This level of exposure would makes it moderately unlikely that the true rate of unwitnessed events is >1% or about 5% per year.

During 12-week, placebo-controlled studies P01:04 and P01:05, deaths on placebo and active treatment were evenly matched in number (approximately 3 per 1000 subject-weeks) and character. All were plausibly related to progression of underlying disease. The death rate during open-label follow-on study P01:06 was a little higher (approximately 5 per 1000 subject-weeks), but the events were similar to those in both treatment groups of studies P01:04 and P01:05.

The most common adverse events that were clearly treatment-related were injection site pain and injection site reaction. This has implications for the quality of life of patients receiving UT-15, and also implications for the quality of blinding in controlled studies. Diarrhea, nausea, vomiting, and jaw pain, all less common than inject site problems, are all highly likely to be related to treatment.

Serious adverse events were common in this population. There was little reason to believe any were related to study drug and not to underlying disease.

There were no apparent effects on laboratory assessments, vital signs, or ECG parameters.

The dose of study drug rose progressively throughout open-label study P01:06, a trend that is not attributable to up-titration of subjects newly receiving UT-15.

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[17] The query for QTc was "SELECT qryQT.TEXT_TRT, [qryqt].[QTc]<450 AS BL, [qryqt_1].[QTc]<450 AS OT, Sum([qryqt_1].[QTc]<450) AS T, Sum([qryqt_1].[QTc]>=450) AS F FROM qryQT INNER JOIN qryQT AS qryQT_1 ON qryQT.PATNUM = qryQT_1.PATNUM GROUP BY qryQT.TEXT_TRT, [qryqt].[QTc]<450, [qryqt_1].[QTc]<450, qryQT.MONVIS, qryQT_1.MONVIS HAVING (((qryQT.MONVIS) Like "S") AND ((qryQT_1.MONVIS) Like "W*"));". Data were from the ECG datasets for both studies, with QTc computed according to Bazett.*

7 Labeling review

The sponsor's proposed label appears in the following pages. The reviewers' proposed changes appear as a red-lined mark-up. Annotations concerning these changes appear in the wide right margin.

PRODUCT INFORMATION

REMODULIN™ (treprostinol sodium)
Injection

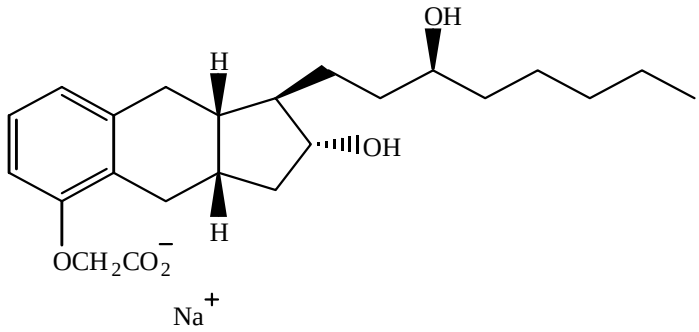
(a) Description

Remodulin (treprostinol sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL or 10.0 mg/mL of treprostinol. Each mL also contains 5.3 mg sodium chloride (except for the 10.0 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, and 6.3 mg sodium citrate. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

~~Treprostinol is a tricyclic benzindene analogue of epoprostenol (prostacyclin, PGI_2) with potent pulmonary and systemic vasodilatory activity. Treprostinol is a potent inhibitor of platelet aggregation *in vitro* and *in vivo*.~~
Treprostinol is chemically stable at room temperature and neutral pH.

Treprostinol is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt. Treprostinol sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

The structural formula of treprostinol is:



(b) Clinical Pharmacology

General: The major pharmacological actions of treprostinol are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinol demonstrated a negative inotropic and lusitropic effect. The

effect of treprostinol on heart rate in animals varies with dose. No major effects on cardiac conduction have been observed.

(1) Pharmacokinetics:

~~In humans, following the initiation of subcutaneous infusion of Remodulin, steady-state plasma concentrations are usually achieved within 15 to 18 hours. Steady-state plasma concentrations of treprostinol are dose-proportional at subcutaneous infusion rates of 2.5 to 15 ng/kg/min; however, it is not known if the proportionality between dose and steady-state plasma levels is maintained at infusion rates greater than 15 ng/kg/min. REMODULIN when administered chronically as a subcutaneous infusion is completely absorbed and has a mean apparent elimination half-life of 3 hours compared to 45 minutes when administered intravenously. The mean volume of distribution and plasma clearance for treprostinol are 1.1 L/kg and 589 mL/kg/hr, respectively.~~

~~In a [^{14}C] treprostinol mass balance and metabolic fate study in healthy volunteers, 78.6% and 13.4% of the subcutaneous radioactive dose were recovered in the urine and feces, respectively, over a period of 224 hours. There was no single major metabolite observed. Five metabolites were detected in the urine, ranging from 10.2% to 15.5%. of the dose administered. These five metabolites accounted for a combined total of 64.4%. Three are products of oxidation of the 3-hydroxyloctyl side chain, one is glucuronide conjugate (treprostinol glucuronide) and one is unidentified. Only 3.7% of the dose was recovered in the urine as unchanged parent drug.~~

~~In a chronic pharmacokinetic study in normal volunteers with chronic subcutaneous Remodulin doses ranging from 2.5 to 15 ng/kg/min, steady state plasma treprostinol concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved trough levels twice (at 7 a.m. and 4 p.m., respectively). The peak concentrations were ~20% to 30% higher than trough concentrations. Dose adjustments are not deemed to be necessary due to diurnal variation.~~

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 µg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 15 ng/kg/min has not been demonstrated.

Absorption: Remodulin is relatively rapidly and completely absorbed with an absolute bioavailability of approximately 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 µg/L.

Distribution: The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at in vitro concentrtions ranging from 330-10,000 µg/L was 91% bound to human plasma protein.

Metabolism: Remodulin is heavily metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described and are labeled HU1 through HU5. The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinol. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A.

Excretion: The elimination of Remodulin is biphasic, with a terminal half-life of approximately 2-4 hours. Approximately 79% of the administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of the dose was excreted in the feces. In urine, each of the identified metabolites was between 10-16% of the administered dose. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

(2) Special Populations:

~~**Hepatic Insufficiency:** An acute study of Remodulin™ administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes was conducted in nine patients with portopulmonary hypertension and stable,mild or moderate hepatic dysfunction. Remodulin was well tolerated and improved cardiopulmonary hemodynamics. Hepatic dysfunction reduced plasma clearance of Remodulin by up to 80% compared to healthy adult volunteers primarily by lowering the volume of distribution without effecting plasma half-life. Remodulin should be increased more conservatively in patients with hepatic dysfunction and these patients should be closely monitored for signs and symptoms or emergence of AEs due to excess Remodulin.~~

~~**Renal Insufficiency:** No studies have been performed in patients with renal impairment. Treprostinol is not excreted to any significant degree by the kidney; however, patients with renal impairment may have different sensitivities (usually increased sensitivity) to agents. Based on the individual patient dose titration recommended for Remodulin, doses of Remodulin should be increased more conservatively in patients with renal insufficiency.~~

~~**Obese Patients:** Obese subjects (BMI greater than 30.0 kg/m^2) clear treprostinol at a slower rate. Since doses of Remodulin are increased from very low initial doses to doses that improve disease symptoms while minimizing adverse effects, dosing to ideal body weight in obese patients should not be necessary.~~

Hepatic insufficiency: In patients with portopulmonary hypertension and mild (n=4) or moderate (n-5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a Cmax that was 2-fold and 4-fold, respectively, and increased AUC $_{0-\infty}$ 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

In patients with mild or moderate insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/min/kg ideal body weight and should cautiously be increased. Remodulin has not been studied in patients with severe heptic insufficiency.

Renal Insufficiency:

Caution should be exercised in the administration of Remodulin to patients with renal insufficiency. Although only 4% of the administered dose is excreted unchanged in the urine, the five isolated metabolites are all excreted in the urine. No studies have been performed in patients with renal insufficiency.

Effect of Other Drugs on Remodulin:

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen- Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven

doses did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Clinical Trials in Pulmonary Arterial Hypertension (PAH):

Hemodynamic Effects: ~~Acute infusion of Remodulin at 10 ng/kg/min intravenously for 75 minutes followed by a 10 ng/kg/min infusion subcutaneously for 150 minutes, in patients with primary pulmonary hypertension produced increases in cardiac index (CI) and mixed venous oxygen saturation (SvO_2), and decreases in mean pulmonary arterial pressure (PAPm) , mean right atrial pressure (RAPm) and pulmonary vascular resistance indexed (PVRI), with little effect on mean systemic arterial pressure (SAPm) or heart rate (HR).~~

I see no study supporting this.

Chronic continuous, subcutaneous infusion of Remodulin in NYHA Class II, III or IV patients with PAH was studied in two identical, 12-week, double-blind, placebo-controlled, multicenter, parallel-group, randomized trials comparing Remodulin plus conventional therapy to conventional therapy alone. Dosage of Remodulin was determined as described in DOSAGE AND ADMINSTRATION and averaged 9.3 ng/kg/min at Week 12. Conventional therapy used to treat patients with PAH included some or all of the following: anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen. The underlying disease process was primary pulmonary hypertension in 58% of those enrolled and pulmonary hypertension secondary to collagen vascular disease (19%) and congenital left to right shunts (23%)in the remaining patients.

~~As t~~(T)he two studies were identical in design and conducted simultaneously, (and the) results were analyzed both pooled and individually. As shown in Table 1, hemodynamic effects after chronic therapy with Remodulin™ ~~were generally consistent with the pharmacological effects seen acutely. There~~ were statistically significant but small. Among those who completed the 12-week study, there were statistically significant increases in CI and SvO_2, and statistically significant decreases in PAPm, RAPm, PVRI and SVRI in patients treated with Remodulin ~~for 12 weeks~~ compared to patients treated with placebo. Heart rate and SAPm were unchanged. ~~In patients with pulmonary hypertension, elevated RAPm and PAPm, and reduced CO and SvO_2 are predictive of mortality.~~

Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)

CI ($L/min/m^2$)	2.37 ± 0.06	2.24 ± 0.05	+0.12 ± 0.04*	-0.06 ± 0.04
PAPm (mmHg)	61.8 ± 1.16	59.9 ± 0.96	-2.3 ± 0.51*	+0.7 ± 0.58
RAP (mmHg)	10.3 ± 0.38	10.0 ± 0.39	-0.5 ± 0.36*	+1.4 ± 0.33
PVRI ($mmHg/L/min/m^2$)	26.51 ± 0.97	25.11 ± 0.87	-3.54 ± 0.64*	+1.20 ± 0.57
SVRI ($mmHg/L/min/m^2$)	37.87 ± 1.05	39.23 ± 1.02	-3.54 ± 0.96*	-0.80 ± 0.85
SvO_2 (%)	61.5 ± 0.70	60.2 ± 0.77	+2.0 ± 0.76*	-1.4 ± 0.65
SAPm (mm Hg)	89.6 ± 0.92	90.7 ± 0.89	-1.7 ± 0.86	-1.0 ± 0.91
HR (bpm)	82.4 ± 0.83	82.1 ± 0.97	--0.5 ± 0.80	-0.8 ± 0.74

*Denotes statistically significant difference between Remodulin and placebo, $p \leq 0.0005$
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular pressure indexed; RAPm = mean right atrial pressure, SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO_2 = mixed venous oxygen saturation, HR = heart rate

Clinical Effects: Exercise capacity, as measured by the six-minute walk test, improved significantly in patients receiving continuous subcutaneous Remodulin plus conventional therapy (N=232) for 12 weeks compared to those receiving conventional therapy plus placebo (N=236) (p=0.0064). Improvements were apparent as early as Week 6 of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Dyspnea-Fatigue Rating and Borg Scale. Signs and symptoms of PAH and Quality of Life also improved.

(c) Indications and Usage

Remodulin™ is indicated for the long-term subcutaneous treatment of Pulmonary Arterial Hypertension in NYHA Class II, III, and IV patients. (see Clinical Pharmacology: Clinical Trials).

(d) Contraindications

Remodulin in contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds

(e) Warnings

Remodulin has been administered intravenously in acute clinical trials ~~with no unexpected adverse effects~~. ~~However~~, to a small number of subjects, but no chronic controlled trials have been performed with intravenous Remodulin therefore it is indicated for subcutaneous use only.

(f) Precautions

(1) General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. ~~Dosage adjustments in clinical trials were based on the patient's signs and symptoms of PAH and side effects of Remodulin. Dosage of Remodulin should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable adverse events associated with Remodulin~~. The decision to initiate therapy with Remodulin should be based on the understanding that there is a high likelihood that subcutaneous therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.
The recommended dosing instructions are based on the algorithm employed during clinical studies. Doses were to be increased predicted on lack of improvement or worsening of symptoms of disease and were decreased based on excessive pharmacologic effects. (see DOSAGE and ADMINISTRATION).

~~The decision to initiate therapy with Remodulin should be based on the understanding that there is a high likelihood that subcutaneous therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered. As with any potent vasodilator~~, [A]~~a~~brupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms (and should be avoided~~)~~. ~~In clinical trials, no patient death from discontinuation of Remodulin was judged attributable to the interruption of Remodulin. Only three of 55 (5%) patients with abrupt disruption of Remodulin developed increased symptoms of PAH, and no patients developed hemodynamic instability. In addition, among patients who discontinued Remodulin abruptly, no relationship has been established between abrupt discontinuation and rebound pulmonary hypertension.~~

(2) Information for patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous catheter, via an infusion pump. The decision to receive Remodulin should be based upon the understanding that therapy with Remodulin will be needed for prolonged periods, possibly years, and the patients ability to accept, place and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

(3) Drug interactions

~~Additional reductions in blood pressure may occur when Remodulin™ is administered with diuretics, anthihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for Remodulin to increase the risk of bleeding. However, patients receiving Remodulin in clinical trials were maintained on anticoagulants without evidence of increased bleeding. No untoward clinical manifestations have been observed in patients in whom~~ Reduction in blood pressure caused by Remodulin may potentially be exacerbated by drugs that by themselves alter blood pressure such as diuretics, antihypertensive agents or vasodilators. Since Remodulin inhibits platelet aggregation, there is the potential for increased risk of bleeding, particularly, among those maintainined on anticoagulants. During clinical trials, Remodulin was used concurrently with the following classes of drugs: anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. Chronic subcutaneous Remodulin administration required concomitant therapies to manage ~~adverse events associated with the use of Remodulin~~infusion site pain. Adverse events associate with these concomitant therapies may occur and should be handled as medically appropriate.

Effect of Other Drugs on Treprostinol

~~The effect of large daily doses of acetaminophen (4g/day) on the kinetics of treprostinol was investigated in a healthy volunteer study. The results demonstrate that acetaminophen does not have any clinically important effect on the pharmacokinetics of treprostinol. Treprostinol did not significantly affect the plasma protein binding of digoxin or warfarin when evaluated in human plasma at physiologic concentrations. In a multivariate analysis of treprostinol plasma clearance values obtained in two controlled trials, 6% of the variability in treprostinol plasma clearance values could be explained by the presence of furosemide (both treprostinol and furosemide undergo glucoronidation at the carboxylate group during metabolism). Based on the modest suggestion of an interaction, a reduction in dose in patients receiving~~

Effect of Other Drugs on Remodulin:

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen- Analgesic doses of acetaminophen, 1000 mg every hours for seven doses did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min .

Effect of Remodulin on Other Drugs

In-vivo studies

Warfarin- Remodulin does not affect the pharmacokinetics or pharmacodymamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous remodulin, 10 mg/kg/min.

~~furosemide is not recommended, although patients should be monitored for excess adverse effects of Remodulin.~~

~~**Effect of Treprostinol on Other Drugs**~~
~~***In Vitro* Studies**~~

~~Results from an *in vitro* study in human hepatic microsomes demonstrated that treprostinol does not significantly inhibit the following P450 isoforms - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In a separate study which investigated the induction effect of treprostinol on rat liver microsomal cytochrome P450 enzymes, treprostinol was found to lack any significant induction effect on (CYP1A), (CYP2B) and (CYP3A).~~

~~*In Vivo Studies*~~

~~Treprostinol had no effect on warfarin pharmacodynamics as measured by the effect on INR. Treprostinol also had no effect on the pharmacokinetics of either the R- or S-enantiomer of warfarin.~~

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen- Analgesic doses of acetaminophen, 1000 mg every hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min .
Effect of Remodulin on Other Drugs
In vivo studies
Warfarin- Remodulin does not affect the pharmacokinetics or pharmacodymamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous remodulin, 10 mg/kg/min.
Hepatic Impairment
The clearance of Remodulin is decreased by up to 80% in patients with mild-moderate hepatic impairment when compared to healthy adults. There is no information in patietns with severe hepatic impairment.. Caution should therefore be exercised during the treatment of these patients with Remodulin.
Renal Insufficiency:
Remodulin should be used with caution in patietns with renal insufficiency. Although Remodulin is not extensively renally excreted, its major metabolites are . There are no studies in patients with renal impairment.

(4) Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies have not been performed to evaluate carcinogenic potential. *In vitro* and *in vivo* mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinol. ~~Treprostinol was not teratogenic in pregnant rats at doses up to 900 ng/kg/min. No developmental~~

~~toxicity was seen in rabbits at 50 ng/kg/min. In reproductive performance studies in rats, treprostinol had no effect on male on female fertility at doses up to 450 ng/kg/min.~~ Treprostinol sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusion at rates of up to 4450 ng trerpstinol/kg/min[about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis.

(5) Pregnancy

Pregnancy Category B ~~No developmental toxicity was seen in rats at any dose of treprostinol up to 900 ng/kg/min and in rabbits at 50 ng/kg/min. In pregnant rabbits, developmental toxicity characterized by minimal increases in fetal skeletal variations per litter was observed at doses of 150 and 300 ng/kg/min and was associated with maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Remodulin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~ In pregnant rats, continuous subcutaneous infusion of treprostinol sodium at rates as high as 900 ng treprostinol/kg/min (about 117 times the starting human rate of infusion, on a ng/m^2 basis and about 16 times the average rate achieved in clinical trials) resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusion on the fetus were limited to an increased incidence of skeletal variations (associated with maternal toxicity) at a rate of 150 ng treprostinol/kg/min (about 41 times the starting human rate of infusion, on a ng/m^2 basis, and 5 times the average rate used in clinical trials). There are no adequate and well-controlled sudies in pregnant women. Remodulin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(6) Nursing mothers

It is not known whether treprostinol is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin™ is administered to nursing women.

(7) Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

(8) Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general,

dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

(g) Adverse Reactions

Interpretation of AEs reported during clinical trials should be undertaken with an awareness of expected events attributable to the progression of the underlying disease, to Remodulin, and/or to the drug delivery system.

~~Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacological effects of Remodulin (e.g., dizziness, syncope).~~ Adverse events that occur during tretment with Remodulin must be interpreted both with respect to the excesses of the effects of drug as well as the with respect to the natural progression of the underlying disease process. Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor. During clinical trials infusion site pain/reaction is the most common adverse event among those treated with Remodulin. Infusion site reaction was defoned as any local adverse event other than pain or bleeding/gruising at the infusion site and include symptoms such as erythema, induration or rash. The pain/reaction Infusion site pain and infusion site reaction were described as severe in 39% and 38% of those enrolled and was the most frequent cause of discontinuation from the studies. During the 12-week study narcotics were dispensed to 32% of those enrolled and antiinflammatory medications were prescribed in 48% of those enrolled to combat infusion site pain or infusion site reaction. ~~Several adverse events can clearly be attributed to Remodulin, the most common of which is pain at the infusion site, tolerated by a majority of patients.~~ Other adverse events include ~~infusion site reaction~~, diarrhea, jaw pain, edema, vasodilatation and nausea. Infusion site reaction was defined as any local adverse event other than infusion site pain or infusion site bleeding/bruising, such as erythema, induration, or rash.

Adverse Events During Chronic Dosing: In an effort to separate the adverse effects of Remodulin™ from those of the underlying disease, Table 2 lists adverse events that occurred at a rate at least 5% more frequently in patients treated with Remodulin than with placebo in controlled trials in PAH.

Table 2: Frequency of Adverse Events Regardless of Attribution Occurring in Patients with PAH with ≥5% Difference Between Remodulin and Placebo in Controlled Studies

Adverse Event	UT- (N=236) N (%)	Placebo (N=233) N (%)
Occurrence More Common with Remodulin		
General (Body as Whole)		
Jaw pain	31 (13.1)	11 (4.7)
Gastrointestinal (Digestive)		
Diarrhea	58 (24.6)	36 (15.5)
Metabolic and Nutritional		
Edema	21 (8.9)	6 (2.6)
Neurological/Nervous		
Vasodilatation	25 (10.6)	11 (4.7)
Skin and Appendages		
Infusion site pain	200 (84.7)	62 (26.6)
Infusion site reaction	196 (83.1)	62 (26.6)
~~Occurrence More Common with Placebo~~		
~~**Hematologic and Lymphatic**~~		
~~Ecchymosis~~	~~9 (3.8)~~	~~27 (11.6)~~
~~**Respiratory**~~		
~~Cough~~	~~7 (3.0)~~	~~19 (8.2)~~
~~**Skin and Appendages**~~		
~~Infusion site bleed/bruise~~	~~79 (33.5)~~	~~102 (43.8)~~

Use 5% cut-off (not 5% difference from placebo, limit to events where drug > PBO]

Table 3 lists all adverse events reported in controlled clinical trials of patients with PAH, that were significantly more frequently encountered in the Remodulin™ group than in the placebo group, regardless of attribution.

Table 3: AEs That Were Significantly (p<0.1) More Frequently Encountered in the Remodulin Group Than in the Placebo Group, Regardless of Attributability

AE Description, as COSTART Preferred Term	Number of events Remodulin-group / placebo group	~~p-value~~	
Any AE	231 / 218	~~0.0173~~	
Infusion site pain	200 / 62	~~<0.0001~~	
Infusion site reaction	196 / 62	~~<0.0001~~	
Diarrhea	58 / 36	~~0.0091~~	
Jaw pain	31 / 11	~~0.0010~~	
Vasodilatation	25 / 11	~~0.0127~~	
Edema	21 / 6	~~0.0026~~	
Anorexia	11 / 4	~~0.0592~~	
Epistaxis	10 / 4	~~0.0904~~	
Nausea and vomiting	7 / 2	~~0.0909~~	
Hypokalemia	5 / 0	~~0.0316~~	
Melena	5 / 0	~~0.0316~~	

Combine Table 2 and 3 and remove p-values, but indicate by bolding those advers events that are nominally p< 0.05.

Adverse Events Attributable to the Drug Delivery System in PAH Controlled Trials: There were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 placebo) reported non-serious adverse events resulting in infusion system complications. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration~~, although in some cases PAH symptoms reappeared.~~

(h) Overdosage

Signs and symptoms of overdose with Remodulin during clinical trials are ~~similar to expected~~ (extensions of its)dose-limiting pharmacological effects(and includes) ~~of Remodulin, including~~ flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in the chronic, uncontrolled trial seven additional patients received an overdose; these occurrences resulted from accidental bolus of Remodulin, errors in pump programmed rate of administration and prescription of incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope). ~~No deaths occurred as a result of overdose.~~

(i) Dosage and Administration

Remodulin™ is supplied in 20 mL vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL(, it is meant to be administered without further dilution).

Initial Dose:

Remodulin is administered by continuous subcutaneous infusion. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments:

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while achieving an acceptable side effect profile. The infusion rate should be adjusted as tolerated based on PAH signs and symptoms and Remodulin side effects. Adverse events include signs and symptoms which reflect excessive pharmacological effects of Remodulin and include headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction.

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion. ~~Dose-related symptoms may necessitate a decrease in infusion rate; however, the event may resolve without dosage adjustment. Should an adverse event~~

~~worsen and/or become intolerable, the infusion rate should be reduced.~~ Abrupt cessation of infusion is to be avoided.

Administration:

Remodulin is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using a infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be able to adjust infusion rates in approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion rates are calculated using the following formula.

Infusion Rate (mL/hr) **= Dose** (ng/kg/min) **x Weight** (kg) **x [0.00006/Remodulin dosage strength concentration** (mg/mL)**]**

Tables 4 through 7 provide Remodulin infusion delivery rates for doses up to 155 ng/kg/min, based on patient weight, drug delivery rate and concentration. These tables may be used to select the most appropriate concentration and infusion rate for Remodulin. No dilution is necessary.

Table 6 5.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mL/hr) for 5.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
10	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
12.5	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
15	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
17.5	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
20	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
22.5	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
25	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
27.5	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
30	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
32.5	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
35	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
37.5	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
40	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
42.5	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
45	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
47.5	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
50	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
55	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
60	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
65	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
70	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
75	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
80	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The infusion rate for 5.0 mg/mL may be calculated using the following formula: Patient Weight(kg) x dose(ng.kg/min) x 0.000012.

Table 7 10.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mLs/hr) for 10.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
50	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
55	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
60	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
65	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
70	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
75	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
80	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
85	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
90	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
95	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
100	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
105	0.022	0.025	0.028	0.032	0.035	0.038	0.041	0.044	0.047	0.050	0.054	0.057	0.060	0.063
110	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
115	0.024	0.028	0.031	0.035	0.038	0.041	0.045	0.048	0.052	0.055	0.059	0.062	0.066	0.069
120	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
125	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
130	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
135	0.028	0.032	0.036	0.041	0.045	0.049	0.053	0.057	0.061	0.065	0.069	0.073	0.077	0.081
140	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
145	0.030	0.035	0.039	0.044	0.048	0.052	0.057	0.061	0.065	0.070	0.074	0.078	0.083	0.087
150	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
155	0.033	0.037	0.042	0.047	0.051	0.056	0.060	0.065	0.070	0.074	0.079	0.084	0.088	0.093

Note: Blank spaces indicate the this concentration of UT-15 is inappropriate for the corresponding dose. The infusion rate for the 10 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/mL) x .000006.

Shaded areas indicate the highest infusion rate supported by one syringe change every three days

Table 6 5.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mL/hr) for 5.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
10	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
12.5	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
15	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
17.5	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
20	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
22.5	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
25	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
27.5	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
30	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
32.5	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
35	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
37.5	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
40	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
42.5	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
45	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
47.5	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
50	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
55	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
60	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
65	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
70	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
75	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
80	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The infusion rate for 5.0 mg/mL may be calculated using the following formula: Patient Weight(kg) x dose(ng.kg/min) x 0.000012.

e 7

10.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mLs/hr) for 10.0 mg/mL UT-15

Patient Weight (kg)

ose g/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
50	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
55	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
60	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
65	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
70	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
75	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
80	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
85	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
90	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
95	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
00	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
05	0.022	0.025	0.028	0.032	0.035	0.038	0.041	0.044	0.047	0.050	0.054	0.057	0.060	0.063
10	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
15	0.024	0.028	0.031	0.035	0.038	0.041	0.045	0.048	0.052	0.055	0.059	0.062	0.066	0.069
20	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
25	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
30	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
35	0.028	0.032	0.036	0.041	0.045	0.049	0.053	0.057	0.061	0.065	0.069	0.073	0.077	0.081
40	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
45	0.030	0.035	0.039	0.044	0.048	0.052	0.057	0.061	0.065	0.070	0.074	0.078	0.083	0.087
50	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
55	0.033	0.037	0.042	0.047	0.051	0.056	0.060	0.065	0.070	0.074	0.079	0.084	0.088	0.093

Note: Blank spaces indicate the this concentration of UT-15 is inappropriate for the corresponding dose. The infusion rate for the 10 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/mL) x .000006.

Shaded areas indicate the highest infusion rate supported by one syringe change every three days

(j) How Supplied

Remodulin™ is supplied in 20 mL multi-use vials at concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL treprostinol, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinol sodium equivalent to 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, or 10.0 mg/mL treprostinol. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F).

During use, a single reservoir of Remodulin can be administered up to 72 hours at 37°C.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostinol sodium equivalent to 1 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 2.5 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 5.0 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinol sodium equivalent to 10.0 mg treprostinol per mL, carton of 1 (NDC xxxx-xxxx-xx).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.
Research Triangle Park, NC 27709

REMODULIN manufactured by

Cook Pharmaceutical Solutions

Bloomington, IN 47403

For United Therapeutics Corp.

Research Triangle Park, NC 27709

8 Summary and recommendations

8.1 Chemistry, microbiology, scientific investigations

The are no issues that should impact on the approvability of UT-15.

8.2 Pharmacology and toxicology

The are no issues that should impact on the approvability of UT-15.

8.3 Biopharmaceutics

The are no issues that should impact on the approvability of UT-15.

There were no data appropriate to address the observed dose escalation.

8.4 Effectiveness

The sponsor's development program was intended to demonstrate a beneficial effect of UT-15 on 6-minute walk in a population with primary or secondary pulmonary hypertension. Three trials contribute to this evaluation.

Study P01:03, only 43 subjects, did not demonstrate a nominally statistically significant effect on walking distance, but there is a trend in favor of UT-15.

Studies P01:04 and P01:05 had the same protocol and they were intended to be analyzed together. The prospective plan for deciding these studies comprised compelling evidence of effectiveness was a $p<0.049$ for each study or $p<0.049$ for one study and $p<0.01$ for the combined analysis. By none of the sponsor's 4 proposed analyses and none of the 4 FDA medical and statistical reviewers' analyses do these trials meet the prospective criteria for effectiveness.

The trend in studies P01:04 and P01:05 is in favor of a benefit for UT-15; the apparent failure to meet the statistical test appears to be attributable to a smaller than expected treatment effect, rather than a wider than expected variance.

Supporting data from the P01:04-05 studies include nominally to highly statistically significant effects of treatment on secondary end points of signs and symptoms (largely chest pain, dizziness, and palpitations), dyspnea-fatigue index (each of the domains of magnitude of task, magnitude of pace, and functional impairment), Borg dyspnea scale, but not on quality of life assessment.

Supportive short-term hemodynamic findings included favorable effects on right atrial pressure, pulmonary arterial pressure, and pulmonary arterial resistance, but unfavorable effects on cardiac output and stroke volume.

During long-term open-label administration, the dose of UT-15 rose progressively, at a rate exceeding that seen in the Flolan development program. Possible explanations for the rising dose include (1) development of tolerance to the effectiveness of UT-15, (2) accommodation to pain associated with UT-15, and (3) disease progression. Existing data do not allow distinguishable among these.

8.5 Safety

Mortality was about 3 per 1000 subject-weeks in both treatment arms of controlled studies and about 5 per 1000 subject-weeks during open label exposure. In none of these events was study drug thought by sponsor or reviewers to be plausibly related to study drug.

Local injection site pain and injection site reactions were clearly more common on UT-15 than on vehicle, but there was no discernible dose-relatedness. On the other hand, it may be that tolerance related to local pain and reaction limits the dose. One manifestation of the injection site problems is the high use of anti-inflammatory agents, opioids, and other pain-relief medications.

8.6 Relationship with Flolan

Flolan is approved for the treatment of patients with primary pulmonary hypertension Class III and IV. However, its use is difficult and inconvenient. The infusion of Flolan requires the insertion of an indwelling central catheter with the attendant risks of the inserting the catheter and the subsequent risk of catheter infection. Flolan has a rapid half-life and rapid dissipation of its hemodynamic effects. Any inadvertent interruption of the infusion is potentially life threatening. Flolan is chemically labile at room temperatures and must be reconstituted every 8 hours or kept at cold temperatures during the infusion. UT-15 was developed to avoid these problems and thereby delay the time till Flolan treatment becomes infusion.

There is no scientific rationale to concurrently use UT-15 with Flolan. There is also no empirical safety or efficacy information on the concurrent use of these drugs. UT-15 is intended as treatment of pulmonary hypertension solely to postpone starting Flolan. There is no study that randomized patients to Flolan or UT-15 that demonstrates equivalent outcomes so that there may be unintended negative consequences in the delay of Flolan infusion. Comparing the labeling of Flolan to the likely labeling of UT-15 the mortality benefit for Flolan does not appear to be uniformly observed with UT-15. The current labeling of Flolan states:

> *"Survival was improved in NYHA functional Class III and IV PPH patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period 8 of 40 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P=0.003)."*

In the pivotal UT-15 studies (P01:04 and P01:05) the drug demonstrated no mortality benefit. The UT-15 study population consisted of predominantly (55%) primary pulmonary hypertension patients with the vast majority NYHA Class III and this portion of the population coincides with the population for which Flolan demonstrated a mortality benefit. There were 9 deaths among those randomized to UT-15 and 10 deaths among those randomized to vehicle during the 12-week study. Five of the 9 deaths on UT-15 were patients with primary pulmonary hypertension while 8 of the 10 deaths on vehicle were patients with primary pulmonary hypertension.

Performance benefit on the 6-minute walk for UT-15 patients was small, approximately 3% of the baseline walk distance. Performance among those with Flolan was approximately 35-50% of baseline walk distance. Admittedly, the basis of comparison is across studies with different designs. Nevertheless, the magnitude of effects a does give one pause before assuming equivalence.

8.7 Recommended regulatory action

An appropriate trend in the exercise data in favor of UT-15 and favorable effects on various measures of symptoms provide reasonable assurance that UT-15 is an effective treatment for pulmonary hypertension, although it falls short of the usual two-trials test and the less stringent prospective analysis plan. A reasonable interpretation of these data is that UT-15 is not very effective, possibly because of difficulties in achieving appropriate doses.

Had the population been a complete overlap with that for Flolan, it would be hard to argue that the small effect of treatment plus the less invasive subcutaneous administration make UT-15 a reasonable alternative to the probably more effective and life-saving Flolan. But the UT-15 study population is somewhat broader, and the comparison with Flolan needs be made cautiously.

The final major consideration is that UT-15 doses rise dramatically with the time of exposure. The explanation for this rise, considerably larger than that seen with Flolan, is not known.

The reviewers conclude that the small benefits of treatment, the lack of effect on mortality, the ominous dose escalation, and the problematic management of injection site pain do not sum to make UT-15 a useful treatment for pulmonary hypertension.

Appendix A Reviews of individual studies.

This section contains reviews of the individual studies comprising the sponsor's development program for UT-15 in pulmonary hypertension. Of the studies submitted with NDA 21-272, only study P01:06, the long-term, open-label extension study, is not represented here. Safety findings from study P01:06 are described in section 6 on page 15.

A.1 Study P01:01: A dose-range-finding study of intravenous 15AU81 (UT-15) patients with primary pulmonary hypertension.

A.1.1 Sites and investigators

P01:01 was conducted at 5 sites in the United States. The investigators are shown in Table 13.

Table 13. Investigators (P01:01).

Site	Investigator
01	Lewis Rubin, MD
02	Robyn Barst, MD
03	Stuart Rich, MD
04	Bruce Brundage, MD
05	Michael McGoon, MD

A.1.2 Background

Initial protocol submitted: 2.3.97

Protocol amendments: 4.7.97, 6.10.97, 7.18.97

These amendments are detailed in the study report. The most relevant of the changes were to exclude the use of anorexiants in the previous 3 months and to retain the enrollment of women of child-bearing potential.

Subject enrollment: 4.16.97 to 1.17.98

A.1.3 Study design

In this multi-center, parallel, sequential, open-label dose-escalation trial, eligible patients underwent cardiac catheterization and then entered a treatment phase, which consisted of five segments: (a) a Flolan dose-ranging segment from 2 ng/kg/min up to maximum tolerated dose of Flolan, (b) an 90 minute Flolan Washout Segment, (c) an IV UT-15 Dosing Segment starting at 5 ng/kg/min and increasing every 30 minutes up to a maximal tolerated dose (MTD) or 120 ng/kg/min, (d) a 90-minute time period when the patients were observed on the maximally tolerated dose of UT-15, and (e) a 120-minute Washout Segment.

Hemodynamics were assessed at the end of each dose increase, then every 15 minutes during the maintenance segment (segment e).

The primary goals of the trial were to collect safety, hemodynamic and pharmacokinetic data on the use of SQ UT-15 in pulmonary hypertension.

A.1.3.1 Objectives

1) To assess the safety, dose-tolerance, and acute hemodynamic effects of UT-15 IV in patients with severe primary pulmonary hypertension.

2) To compare the hemodynamic profile of UT-15 to Flolan using physiologic responses.

3) To attempt to estimate the apparent half-life of UT-15.

A.1.3.2 Number of subjects/ randomization

Fifteen (15) patients with pulmonary hypertension were enrolled into the study: 14 completed both Flolan and UT-15 infusions.

A.1.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥ 12 years of age;

- Females must be post-menopausal or surgically sterile, or if female of child bearing potential, had a negative pregnancy test;
- had a diagnosis of severe, symptomatic primary pulmonary hypertension (PPH) and were classified NYHA Class III or IV at Screening/Baseline;
- had a chest radiograph consistent with the diagnosis of PPH performed within the previous six months;
- had pulmonary function tests consistent with the diagnosis of PPH performed within the previous year;
- had a pulmonary ventilation/perfusion scan or pulmonary angiography performed since the onset of symptoms with results consistent with the diagnosis of PPH;
- had an echocardiogram within previous year consistent with the diagnosis of PPH, specifically: evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis;
- had a cardiac catheterization at Baseline consistent with the diagnosis of PPH, specifically:

  PAPm ≥ 25 mmHg, and PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and PVR > 3 mmHg/L/min, and absence of congenital heart disease (including atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage, but presence of a patent foramen ovale would not exclude a patient);
- had indicated willingness to participate by signing an informed consent form.
- no drugs for PPH discontinued in previous week except anticoagulants.

Exclusion criteria (may not be present)

- had a new type of chronic therapy (e.g., a different category of oral vasodilator, a diuretic, digoxin) for PPH added within the last month, excepting anticoagulants;
- had any PPH medication, excepting anticoagulants, discontinued within the last week;
- had any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis, portal hypertension, or human immunodeficiency virus infection); or
- were currently receiving an investigational drug or have participated in investigational drug study within the past 30 days;

A.1.3.4 Dosage/ administration

UT-15 and Flolan were administered IV through a central venous catheter.

Concomitant medications. Drugs routinely used for PPH patients, including calcium channel blockers, digoxin, diuretics, anticoagulants and oxygen were provided by the hospital pharmacy and administered as deemed appropriate by each investigator. Prostacyclin analogues were not allowed as therapy.

A.1.3.5 Duration/ adjustment of therapy

Study drug was administered in hospital, and where patients remained throughout the drug administration and for 24 hours thereafter.

A.1.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.16. Invasive hemodynamic measurements were made during the period of the infusions and at the end of the washout period along with pharmacokinetic sampling and routine vital signs. After washout and through the first 24 hours vital signs and ECGs were collected every 8 hours.

A.1.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.1.4 Results

A.1.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were white (73%) and female (87%), with a mean age of 35 and a mean duration since diagnosis of PPH of 0.9 years. The majority (14/15, 93%) were NYHA Class III and the remaining one subject was NYHA Class IV. The reader is referred to the study report for additional demographics.

A.1.4.2 Disposition of subjects

Of the 15 patients enrolled, one patient was discontinued for an adverse event (vasovagal reaction) during the baseline phase of the study and 4 were discontinued during the maintenance phase (phase e). These last 4 patients are discussed in Safety below.

Subject selection. No information is available about subject selection in protocol P01:01.

Protocol violations & deviations. No significant protocol violations occurred.

Concomitant therapies. Given the short duration of the trial no concomitant medications were used during the administration of the study drug.

A.1.4.3 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nguyenand Gobburu. The sponsor estimated the half-life of subcutaneous UT-15 at between 55 to 117 minutes, and the half-life for the IV form of UT-15 as 25 to 42 minutes.

A.1.4.4 Hemodynamic changes

Table 14 below summarizes the hemodynamic changes from baseline for Flolan and UT-15. A total of 14 patients completed the dose-ranging parts of the study are their data are used for these comparisons. A total of 10 patients completed the maintenance phase and their data are included in this par of the summary. Baseline is taken as the last value before starting the infusion of Flolan or UT-15.

Table 14. Baseline hemodynamic parameters (P01:01)[18]

	Flolan N=14	UT-15 N=14
HR (bpm)	83±4	81±3
Right Atrial Press (mmHg)	10±1	11±1
Cardiac Index	2.5±0.1	2.7±0.3
Pulmonary Artery Press (mm Hg)	56±5	55±5
PVRI (mmHg/L-min-m^2)	19±2	18±3
SVRI (mmHg/L-min-m^2)	37±5	31±3
SvO_2 (%)[19]	66±3	66±3

Table 15 below summarizes the change from baseline for the same parameters. There was a consistent acute effect to increase cardiac index (CI) and decrease pulmonary vascular resistance index (PVRI). No clear dose-related effect on any of the measured parameters was demonstrated.

Table 15. Change from baseline in hemodynamic parameters (P01:01)[20]

	Flolan MTD[21] N=14	UT-15	
		MTD N=14	Maint N=10
HR (bpm)	+10±3%	+8±2%	-1±5%
Right Atrial Press (mmHg)	-10±6%	-19±6%	-39±11%
Cardiac Index	+32±9%	+26±12%	+27±17%
Pulmonary Artery Press (mm Hg)	-1.6±2%	-0.6±3%	-9±3%
PVRI (mmHg/L-min-m^2)	-22±5%	-14±7%	-20±9%
SVRI (mmHg/L-min-m^2)	-26±5%	-8.5±8%	-6±10%
SvO_2 (%)	—	—	+8±5%

Hemodynamic changes during washout. Patients were followed for 120 minutes after discontinuation of UT-15 with hemodynamic measurements. During that period the hemodynamic changes seen during UT-15 did not return to baseline (see table 14.2.3 in study report for details). No patient had rebound pulmonary hypertension during the 120 minutes after UT-15 discontinuation.

Maximum tolerated doses of UT-15. The table below summarizes the MTD of UT-15 for the patients who completed the initial UT-15 infusions, as well as the patients who completed the maintenance phase of the UT-15 infusion. The four subjects who discontinued were receiving different doses of UT-15. However, most of the patients at the higher doses of UT-15 were either discontinued or had to have their dose reduced.

[18] *Data from NDA vol. 2.16, table 11.4.1A.*

[19] *Mixed venous O_2 saturation.*

[20] *Data from NDA vol. 2.16, table 11.4.1C.*

[21] *Maximally tolerated dose*

Table 16. Dosing of UT-15 (P01:01)[22]

Dose	Initiation of maintenance	Completion of maintenance	Completion without dose reduction
5	1	1	1
10	5	4	4
20	1	0	0
30	3	2	0
40	3	3	1
60	1	0	0
All doses	14	10	6

A.1.4.5 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs are shown in Table 17.

Table 17. Disposition of subjects (P01:01)[23]

Event	N
Initiated UT-15	14
Completed initial infusion	14
Discontinued with adverse event	4
Serious adverse event	0
Deaths	0

A.1.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.1.4.5.2 Comments on specific safety parameters

Deaths. There were no deaths reported for subjects in the trial.

Serious adverse events. No SAEs occurred during the administration of study drug.

Adverse events. Table 18 below summarizes the reported AEs.

Table 18. Subjects with adverse events on UT-15 (P01:01).[24]

Event	N (%)
Headache	13 (52%)
Infusion site reaction	4 (16%)
Flushing	8 (32%)
Nausea	4 (16%)
Dizziness	2 (8%)

Discontinuations. There were four discontinuations during the maintenance phase of the UT-15 infusion. Three of these were for nausea, headache and or vomiting. The fourth patient experienced pulmonary hypertension and is detailed below.

Subject 02005 had four SAEs: pulmonary hypertension, atelectasis, bronchitis and pneumonia.

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[22] *Data from NDA vol. 2.16, table 12.1.3.*

[23] *Data from NDA 21-272, vol. 2.16, section 12.1.3.*

[24] *Data from NDA 21-272, table 12.2.2.2B.*

This 12-year old girl with Class III CHF was hospitalized for evaluation. At baseline her pulmonary pressures were 152/68, mean 102 mmHg, exceeding her systemic arterial BP (mean 81 mmHg). Following initiation of UT-15 her cardiac output and systemic pressure rose, and her pulmonary pressures fell. She achieved a dose of UT-15 of 80 ng/kg/min, where she had a dose-limiting side effect of agitation and restlessness. She was then entered into the maintenance phase at 69 ng/kg/min. After 35 minutes her PAP rose abruptly to 218/147 and arterial saturation fell to 75%. Treatment was stopped, and patient received milrinone and O_2 with slow resolution of the elevated PAP. The investigators felt that her cardiac left-to-right shunt, along with her agitation, contributed to the pulmonary hypertensive crisis.

Effects on ECG. Review of the summary data from the ECGs collected during the trial showed no pattern of QT prolongation independent of heart rate. See NDA vol. 2.18, table 16.2.8.4 for details.

A.1.5 Summary

A.1.5.1 Efficacy summary

Study P01:01 measured the acute hemodynamic effects of UT-15 in patients with Primary Pulmonary Hypertension. Samples were also collected for pharmacokinetic assessments. The changes measured in this open-label trial were consistent with an acute effect of UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. The pharmacokinetic assessment will be performed by other reviewers.

A.1.5.2 Safety summary

There were no new safety concerns identified in this small study. One potentially useful observation was that no evidence for rebound hypertension was seen in the 120 minutes following UT-15 discontinuation.

A.1.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of UT-15 to cause pulmonary vascular dilatation. No clear dose-relationship for this effect was demonstrated. Doses higher than 10 ng/kg were not tolerated without dose reduction in this short-term trial, most commonly due to headaches, nausea and/or vomiting. No new safety concerns emerged from this small trial.

A.2 Study P01:02: A dose-range-finding study comparing intravenous and subcutaneous 15AU81 (UT-15) in NYHA Class III/IV patients with primary pulmonary hypertension.

A.2.1 Sites and Investigators

P01:02 was conducted at 10 sites in the United States. The investigators are shown in Table 19.

Table 19. Investigators (P01:02)

Site	Investigator	Site	Investigator
01	Sean Gaine, MB	06	David Badesch, MD
02	Robyn Barst, MD	07	Ivan Robbins, MD
03	Stuart Rich, MD	08	Victor Tapson, MD
04	Bruce Brundage, MD	09	Adaani Frost, MD
05	Michael McGoon, MD	10	Robert Bourge, MD

A.2.2 Background

Initial protocol submitted: 6.18.97

Protocol amendments: one

Amendment #1, submitted on 12.22.97, enrolled 7 additional patients to Cohort II following the completion of Cohort III. Cohort III (20 ng/kg/min SQ dose), was deemed the maximum tolerated acute dose by the sponsor. The enrollment of seven additional patients to Cohort II resulted in a total of 13 patients completing the 10 ng/kg/min dose.

Subject enrollment: 10.4.97 to 1.27.98

Case report form cutoff: 4.29.94

A.2.3 Study design

In this multi-center, parallel, sequential, open-label dose-escalation trial, eligible patients underwent cardiac catheterization and then entered a treatment phase, which consisted of four segments: (a) an IV UT-15 75-minute Dosing Segment, (b) an IV UT-15 150 minute Washout Segment, (c) a subcutaneous (SQ) UT-15 150-minute Dosing Segment (see below for doses), and (d) a SQ UT-15 150-minute Washout Segment.

During the sub-cutaneous (SQ) period of the trial, subjects received IV dosing at 10 ng/kg/min followed by one of three SQ doses:

1) 5 ng/kg/min (n=6 subjects)

2) 10 ng/kg/min (n=13 subjects), or

3) 20 ng/kg/min (n=6 subjects).

The primary goals of the trial were to collect safety, hemodynamic and pharmacokinetic data on the use of SQ UT-15 in pulmonary hypertension.

A.2.3.1 Objectives

To characterize the pharmacokinetic profile of subcutaneous (SQ) administration of UT-15 in patients with severe primary pulmonary hypertension (PPH).

A.2.3.2 Number of subjects/ randomization

Twenty-five (25) patients with pulmonary hypertension were enrolled into the study: 6 each at the 5 and 20 ng/kg/min dose and 13 at the 10 ng/kg/min dose.

A.2.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥ 12 years of age;
- Females must be post-menopausal or surgically sterile, or if female of child bearing potential, had a negative pregnancy test;
- had a diagnosis of severe, symptomatic PPH and were classified NYHA Class III or IV at Screening/Baseline;
- had a chest radiograph consistent with the diagnosis of PPH performed within the previous six months;
- had pulmonary function tests consistent with the diagnosis of PPH performed within the previous year;
- had a pulmonary ventilation/perfusion scan or pulmonary angiography performed since the onset of symptoms with results consistent with the diagnosis of PPH;
- had an echocardiogram within previous year consistent with the diagnosis of PPH, specifically: evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis;
- had a cardiac catheterization at Baseline consistent with the diagnosis of PPH, specifically:

  PAPm ≥ 25 mmHg, and PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and PVR > 3 mmHg/L/min, and absence of congenital heart disease (including atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage, but presence of a patent foramen ovale would not exclude a patient);
- had indicated willingness to participate by signing an informed consent form.

Exclusion criteria (may not be present)

- had a new type of chronic therapy (e.g., a different category of oral vasodilator, a diuretic, digoxin) for PPH added within the last month, excepting anticoagulants;
- had any PPH medication, excepting anticoagulants, discontinued within the last week;
- had any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis, portal hypertension, or human immunodeficiency virus infection); or
- were currently receiving an investigational drug or have participated in investigational drug study within the past 30 days;

A.2.3.4 Dosage/ administration

UT-15 was administered IV or via sub-cutaneous infusion placed in the abdominal wall. After right-heart catheterization and baseline hemodynamic parameters, subjects received IV dosing at 10 ng/kg/min min followed by a SC dose of

1) 5 ng/kg/min (n=6 subjects)

2) 10 ng/kg/min (n=13 subjects), or

3) 20 ng/kg/min (n=6 subjects).

Concomitant medications. Drugs routinely used for PPH patients, including calcium channel blockers, digoxin, diuretics, anticoagulants and oxygen were provided by the hospital pharmacy and administered as deemed appropriate by each investigator. Prostacyclin analogues were not allowed as therapy.

A.2.3.5 Duration/ adjustment of therapy

Study drug was administered in hospital, and where patients remained throughout the drug administration and for 24 hours thereafter.

A.2.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.19. Invasive hemodynamic measurements were made during the period of the infusions and at the end of the washout period along with pharmacokinetic sampling and routine vital signs. After washout and through the first 24 hours vital signs and ECGs were collected every 8 hours.

A.2.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.2.4 Results

A.2.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were white (72%) and female (80%), with a mean age of 40 and a mean duration since diagnosis of PPH of 0.9 years. The majority (19/25) were NYHA Class III and the remainder NYHA Class IV. The reader is referred to the study report for additional demographics.

A.2.4.2 Disposition of subjects

Of the 25 patients enrolled, 10 patients had to terminate either the 75-minute iv infusion or the 150-minute SQ infusion prematurely due to intolerability or technical problems. Hence, only 15 patients completed both the iv and SQ infusions in their entirety.

Subject selection. No information is available about subject selection in protocol P01:02.

Protocol violations & deviations. Patient 04002 received 20 ng/kg/min due to staff error. His course will be discussed in the safety section of this review.

Concomitant therapies. Given the short duration of the trial no concomitant medications were used during the administration of the study drug.

A.2.4.3 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nguyenand Gobburu. The sponsor estimated the half-life of subcutaneous UT-15 at between 55 to 117 minutes, and the half-life for the IV form of UT-15 as 25 to 42 minutes.

A.2.4.4 Hemodynamic changes

Table 20 below summarizes the hemodynamic changes from baseline for the IV and SC administration of UT-15. Baseline is taken as the last value before starting the infusion, either following baseline hemodynamics (for the IV) or at the end of the 150 minute washout period (for the SC). The data from patient 04002 are not included here. Of the 25 patients enrolled, 10 patients had to terminate either the 75-minute iv infusion or

the 150-minute SQ infusion prematurely due to intolerability or technical problems (see Safety below). Hence, only 15 patients completed both the iv and SQ infusions in their entirety (and have data available for inclusion into Table 20 below).

Table 20. Baseline hemodynamic parameters (P01:02)[25]

	IV N=24	UT-15 SC dose (ng/kg/min)		
		5 N=6	10 N=13	20 N=6
HR (bpm)	85±2	88±7	82±2	86±7
Right Atrial Press (mmHg)	10.2±1	10.2±2	10.2±2	13.3±3
Cardiac Index	2.1±0.1	2.0±0.2	2.0±0.2	2.0±0.3
Pulmonary Artery Press (mm Hg)	63±4	65±8	65±6	69±5
PVRI (mmHg/L-min-m^2)	28±4	30±5	30±6	27±4
SVRI (mmHg/L-min-m^2)	45±4	47±3	45±5	47±9
SvO_2 (%)[26]	59±2	59±6	56±4	56±3

Table 21 below summarizes the change from baseline for the same parameters. There was a consistent acute effect to increase cardiac index (CI) and decrease pulmonary vascular resistance index (PVRI). No clear dose-related effect on any of the measured parameters was demonstrated.

Table 21. Change from baseline hemodynamic parameters (P01:02)[27]

	IV N=24	UT-15 SC dose (ng/kg/min)		
		5 N=6	10 N=13	20 N=6
HR (bpm)	-0.6±2.0%	+2.3±3.2%	+0.2±1.9%	+0.9±5.8%
Right Atrial Press (mmHg)	+6.7±13%	+26.7±30%	-19.6±13%	+13.0±37%
Cardiac Index	+12.1±4%	+6.5±7%	+19.4±6%	+7.4±2%
Pulmonary Artery Press (mm Hg)	-5.2±2%	+4.3±3%	-13.4±3%	-7.8±5%
PVRI (mmHg/L-min-m^2)	-17.1±4%	+1.6±13%	-26.6±7%	-15.5%
SVRI (mmHg/L-min-m^2)	-10.4±4%	-4.6±4%	-13.9±4%	-14.4±12%
SvO_2 (%)	+8.0±4%	-1.1±4%	+6.2±2%	+6.0±14%

Rebound hypertension. No evidence of rebound hypertension was seen during the 150 minutes following the discontinuation of UT-15. The vasodilatation persisted to the 150 minute timepoint following discontinuation of UT-15, limiting the usefulness of this data in ruling out a rebound phenomenon. Data for the 10 ng/kg/min dose group is shown below as representative.

[25] *Data from NDA vol. 2.19, table 11.4.1A.*

[26] *Mixed venous O_2 saturation.*

[27] *Data from NDA vol. 2.19, table 11.4.1C.*

Table 22. Baseline, peak, and end-of-washout hemodynamic parameters (P01:02)[28]

	Baseline	End of	
		Infusion	Washout
Right Atrial Press (mmHg)	10.8	8.3	8.1
Cardiac Index	1.9	2.2	2.3
Pulmonary Artery Press (mm Hg)	67.3	58.8	60.9
PVRI (mmHg/L-min-m^2)	31.4	22.3	22.5

A.2.4.5 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 23. Disposition of subjects (P01:02)[29]

	UT-15 SQ (ng/kg/min)		
	5 N=6	10 N=13	20 N=6
Initiated UT-15	6	13	6
Completed 150 min infusion	5	12	3
Discontinued with adverse event	1	1	3
Serious adverse event[30]	0	0	0
Deaths[31]	0	0	0

A.2.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.2.4.5.2 Comments on specific safety parameters

Deaths. Two deaths occurred within three days of discontinuation from the trial.

Subject 02005 completed the trial without problems, and remained in the hospital for a Hickman catheter to be placed for Flolan initiation. After placement of the Hickman, the patient remained in the hospital, and was found cyanotic and pulseless that night. Flolan was not initiated.

Subject 04004 with PPH (NYHA Class III) completed the trial without complications and then received a Hickman to start Flolan. Flolan was initiated without difficulty at a dose of 4 ng/kg/min. The patient was readmitted the next day with worsening CHF and had a bradycardic then asystolic arrest and died.

Serious adverse events. No SAEs occurred during the administration of study drug.

Adverse events. Table 24 below summarizes the reported AEs.

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[28] *Data from NDA vol. 2.19, table 11.4.1.5 and 16.2.6.1. Shown for the SQ 10 ng/kg/min group.*

[29] *Data from NDA 21-272, table 12.1.1A and narratives.*

[30] *One SAE occurred before initiation of infusion of study drug.*

[31] *Two deaths occurred 8 hours and 3 days after dismissal from the study. See section below for details.*

Table 24. Subjects with adverse events (P01:02)[32]

Event	N (%)
Headache	13 (52%)
Infusion site reaction	4 (16%)
Flushing	8 (32%)
Nausea	4 (16%)
Dizziness	2 (8%)

ECGs and vital signs. No effect of UT-15 on ECG parameters, including the QT interval, was seen. See vol. 2.21, table 16.2.8.4 for details. Following administration of UT-15 the heart rate rose by a mean of 3.3 bpm, and the mean blood pressure fell by 6.8/8.7 mmHg (table 16.2.8.3).

A.2.5 Summary

A.2.5.1 Efficacy summary

Study P01:02 measured the acute hemodynamic effects of UT-15 in patients with Primary Pulmonary Hypertension. Samples were also collected for pharmacokinetic assessments. The changes measured in this open-label trial were consistent with an acute effect of UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. The pharmacokinetic/ pharmacodynamic assessment will be performed by other reviewers.

A.2.5.2 Safety summary

There were no new safety concerns identified in this small study. One observation was that no evidence for rebound hypertension was seen in the 150 minutes following UT-15 discontinuation. Unfortunately, the fact that vasodilatation persisted for the period of measurement limits the usefulness of this observation.

The two deaths occurring so shortly after completion of the trial are of concern, especially the death that occurred the night after completion, before Flolan was initiated. While no evidence implicating the drug exists, the timing raises concerns about changes that occurred following discontinuation of UT-15 such as hemodynamic changes or shifts in fluids or electrolytes.

A.2.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of UT-15 to cause pulmonary vascular dilatation. No clear dose-relationship for this effect was demonstrated. No new safety concerns were identified, but two deaths occurred soon after drug discontinuation. These deaths will be considered in the context of the integrated safety summary elsewhere.

[32] *Data from NDA 21-272, table 12.2.2.2B.*

A.3 Study P01:03: A multicenter, double-blind, randomized, parallel comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with severe primary pulmonary hypertension: an 8-week study.

A.3.1 Sites and investigators

P01:03 was conducted at 5 sites in the United States. The investigators are shown in Table 25.

Table 25. Investigators (P01:03).

Site	Investigator
01	Sean Gaine, MB
02	Robyn Barst, MD
03	Stuart Rich, MD
04	Ronald Oudiz, MD & Shelley Shapiro, MD
10	Robert Bourge, MD

A.3.2 Background

Initial protocol submitted: 2.25.98

Protocol amendments: 4.21.98 and 6.16.98

Amendment #1 (4.21.98) reduced the number of pharmacokinetic blood samples collected.

Amendment #2 (6.16.98) lowered the starting dose (i.e., from 5 ng/kg/min to 2.5 ng/kg/min or below) and the in-hospital dose increment from 5 ng/kg/min to 2.5 or 5 ng/kg/min. This change resulted in a reduction in the maximum achievable doses at the end of Week 1 through Week 8 of the Treatment Phase

These changes resulted in a lower number of UT-15 concentration values per patient for pharmacokinetic analysis, resulting in a less precise pharmacokinetic analysis.

Subject enrollment: 4.23.98 to 10.7.98

Case report form cutoff: 4.29.94

The safety and efficacy results of the study were presented at the 1999 European Congress of Cardiology and published in abstract form[33].

A.3.3 Study design

Eligible patients were randomized (2:1) to receive conventional therapy plus a continuous subcutaneous infusion of UT-15 or conventional therapy plus a continuous subcutaneous infusion of placebo for an 8-week infusion period. During the Treatment Phase, in addition to efficacy measurement (exercise capacity) and assessment of clinical signs and symptoms of the disease at scheduled visits (Weeks 1, 4 and 8), blood samples were collected for pharmacokinetic analysis. Hemodynamic and symptom assessments were not available to the individual who conducted the primary efficacy analysis (6-minute walk). Similarly, the walk results were only known by an independent exercise administrator.

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[33] *McLaughlin V, Barst R, Rich S,* et al. *Efficacy and safety of UT-15, a prostacyclin analogue, for primary pulmonary hypertension.* Eur Heart J *1999; **20** (Abstr Suppl):486.*

A.3.3.1 Objectives

1) The primary objective of this study was to assess the safety of continuous subcutaneous infusion of UT-15 in an out-patient environment to patients with primary pulmonary hypertension (PPH).

2) The secondary objective of this study was to characterize the pharmacokinetic disposition of chronic, subcutaneous administration of UT-15 in this patient population.

3) Exercise, hemodynamics and symptoms of disease were monitored, including invasive hemodynamic measurements were made at baseline and week 8.

The primary efficacy end-point was exercise capacity (6-minute walk) at weeks 1, 4 and 8. Additional efficacy measurements included changes in the signs and symptoms of pulmonary hypertension and heart failure, including the Borg Dyspnea Scale and the Dyspnea-Fatigue Rating.

Pharmacokinetic evaluation focused on the plasma UT-15 concentration versus time profiles in individual patients.

A.3.3.2 Number of subjects/ randomization

Twenty-six (26) patients with PPH were enrolled into the study: 17 received UT-15, 9 received placebo.

A.3.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥8 years of age;
- If female, be physiologically incapable of child bearing or practicing an acceptable method of birth control;
- have a diagnosis of severe, symptomatic PPH and remain NYHA Class III or IV despite the use of chronic oral vasodilators for at least one month;
- have a chest radiograph consistent with the diagnosis of PPH performed within the previous six months;
- have pulmonary function tests consistent with the diagnosis of PPH performed within the previous year;
- have a ventilation perfusion scan or pulmonary angiography consistent with the diagnosis of PPH;
- have an echocardiogram within previous year consistent with the diagnosis of PPH, specifically: evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis;
- have hemodynamics consistent with PPH, specifically:
  - PAPm ≥ 25 mmHg, and
  - PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and
  - PVR > 3 mmHg/L/min, and
- Absence of congenital heart disease (atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage);
- be mentally and physically capable of learning to administer study drug using an infusion pump and a subcutaneous access;

- signed informed consent.

Exclusion criteria (may not be present)

- be pregnant (women of childbearing potential must have a negative pregnancy test);
- have a new type of chronic therapy (other than anti-coagulation) for PPH added within the last month;
- have any oral PPH medication excepting anticoagulants discontinued within the last week;
- received any chronic prostaglandin or prostaglandin analogue therapy (IV or inhaled) within the past 30 days;
- have any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis, portal hypertension, HIV);
- have a musculoskeletal disorder (e.g., arthritis, artificial leg, etc.) or any other disease which could limit ambulation, or be connected to a machine which was not portable;
- have a baseline exercise capacity of less than 50 meters or greater than 450 meters walked in six minutes;
- be receiving an investigational drug or have participated in investigational drug study within the past 30 days;
- have the presence of any physiological condition which contraindicates the administration of UT-15.

A.3.3.4 Dosage/ administration

UT-15 or placebo was administered via sub-cutaneous infusion. Of the 17 patients randomized to receive UT-15, only one patient received a starting dose of 5 ng/kg/min. Fifteen 15 patients received a starting dose of 2.5 ng/kg/min and one patient received a starting dose of 1 ng/kg/min.

Study drug was administered subcutaneously using a positive pressure MiniMed (Model 506) microinfusion infusion pump. The subcutaneous catheter was placed in the abdominal wall of patients, and the infusion site was moved, if needed, at the discretion of the investigator. There was to be no washout period between changes in UT-15 infusion rates (doses).

The original starting dose was to by 5 ng/kg/min, but the protocol was amended to a starting dose of 2.5 ng/kg/min.

Concomitant medications. Short-terms (<5 days) of therapy with other agents to treat CHF were permitted with the exception of prostacyclin (Flolan) and its analogues. All other agents were permitted in both treatment groups.

Duration/ adjustment of therapy

Study drug was started in hospital, and where patients remained for the first week to assure stabilization. Study drug was up-titrated weekly to maximum tolerated dose. If a dose was not tolerated, it could be decreased to the maximum tolerated dose for each patient.

A.3.3.5 Safety and efficacy endpoints measured

Table 26. Timetable for clinical observations and lab measurements (P01:03)[34]

	Screen	Baseline		Treatment			
		Week 0		Week 1	Week 4	Week 8	
		Day 1	Day 2	Day 9	Day 29	Day 58	Day 59
Informed consent	X						
Inclusion/exclusion criteria	X		X				
Clinical chemistry/hematology[35]		X				X	
Medical history/physical exam	X						
PPH signs and symptoms[36]/dyspnea-fatigue[37]		X		X	X	X	

[34] *Data from table 9.5.1 from P01:03 Clinical Study Report.*

[35] *See Clinical report for P01:03, section 9.5.2.1 for list of labs measured.*

[36] *Evaluation of PPH signs and symptoms was conducted for each study patient at Baseline and Weeks 1, 4, and 8. To ensure consistency, these parameters were evaluated by the same physician for a given patient throughout the study. The following relevant PPH signs and symptoms were assessed as present or absent; severity, extent or grade was evaluated as shown:*

Loud P2 sound	Dyspnea at rest
Right ventricular S3 sound	Dyspnea on exertion
Right ventricular S4 sound	Paroxysmal nocturnal dyspnea
Right ventricular heave	Dizziness (extent)
Murmur of tricuspid insufficiency (grade)	Syncope (extent)
Murmur of pulmonic insufficiency (grade)	Chest pain (extent)
Hepatomegaly (extent)	Palpitations (extent)
Jugular venous distention at 45 degrees (extent)	Fatigue
Edema (extent)	Orthopnea (severity)

For each patient at Weeks 1, 4, and 8, each parameter was assigned a change score as follows:

Baseline	Treatment Phase	Change Score
Absent	Present	-1
Present	Present	0
Absent	Absent	0
Present	Absent	+1

A composite change score for each assessment period (Week 1, Week 4, or Week 8) was calculated for each patient by adding change scores of the individual signs and symptoms.

[37] *The Dyspnea-Fatigue Rating was assessed at Baseline and Weeks 1, 4, and 8 by study staff that were responsible for patient care. This clinical index of dyspnea and fatigue consists of three components, each rated on a scale of 0 to 4 (worst to best), for* magnitude of the task *that evokes dyspnea or fatigue, the* magnitude of the pace *(or effort) with which the task is performed, and the associated* functional impairment *in general activities. The ratings for each component are added to form an aggregate score, which can range from 0 (for the worst condition) to 12 (for the best).*

The ratings for the three components of the Dyspnea-Fatigue Rating are:

1. Magnitude of task (at normal pace):

4 Extraordinary. *Becomes short of breath or fatigued (hereafter called "symptomatic") only with extraordinary activity such as carrying very heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks.*

3 Major. *Becomes symptomatic only with such major activities as walking up a steep hill, climbing more than three flights of stairs or carrying a moderate load on the level.*

2 Moderate. *Becomes symptomatic with moderate or average tasks such as walking up a gradual hill, climbing less than three flights of stairs or carrying a light load on level ground.*

1 Light. *Becomes symptomatic with light activities, such as walking on the level, washing or standing.*

	Screen	Baseline		Treatment			
		Week 0		Week 1	Week 4	Week 8	
		Day 1	Day 2	Day 9	Day 29	Day 58	Day 59
Exercise capacity[38]/Borg dyspnea[39]		X	X[40]	X	X	X	
Invasive hemodynamic measurements			X				X
Randomization (2:1)			X[f]				
12-lead ECG	X					X	
Pharmacokinetic blood samples[41]			X	X	X	X	
Infusion of study drug/chronic infusion				X	X	X	X
Concomitant medication report	X	X	X	X	X	X	X
Adverse event report	X	X	X	X	X	X	X

The six-minute walk was assessed along a level, limited-access corridor with a minimum length of 33 meters. The test area was marked with gradations to permit distance calculation of partial laps. At a given center, the walk test was to be conducted by the same test administrator, who was otherwise uninvolved in the study or care of the study patients and was blinded to the treatment assignment.

A.3.3.6 Statistical considerations

Power. Trial P01:03 had limited enrollment, and was conducted to provide safety data and to characterize the pharmacokinetics of UT-15. In addition, the sponsor used it to provide estimates of between-treatment changes (and associated variances) of exercise

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0 None. *Symptomatic at rest, while sitting or lying down.*

2. Magnitude of pace:

4 Extraordinary. *Essentially all conceivable physical tasks are performed at normal pace.*

3 Major. *Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Less strenuous tasks can be done at normal pace.*

2 Moderate. *Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal pace.*

1 Light. *Light tasks are done at a reduced pace.*

0 None. *Symptomatic at rest.*

3. Functional impairment:

4 None. *Can carry out usual activities and occupation (if employed before onset of PPH) without symptoms.*

3 Slight. *Distinct impairment in at least one activity but no activities completely abandoned. A change in activity may have occurred at work or in other activities, but the change is slight or is not clearly caused by shortness of breath or fatigue.*

2 Moderate. *Patient has changed jobs or has abandoned at least one usual activity.*

1 Severe. *Patient is unable to work or has given up most or all usual activities.*

0 Very severe. *Unable to work and has given up most or all usual activities.*

[38] *Assessed using the 6-minute walk test.*

[39] *The Borg Dyspnea Scale is a continuous scale from 0 (no dyspnea) to 10 (maximum dyspnea) indicating the maximal shortness of breath experienced by a patient during performance of the Six-Minute Walk Test (Baseline and Weeks 1, 4, and 8). A standardized script was used in the assessment. The data from the exercise test and Borg Dyspnea Scale were then recorded directly onto the appropriate CRF and were not available to the other study staff.*

[40] *Used as baseline for later comparisons.*

[41] *Blood samples for pharmacokinetic collected pre dose increase, and 30, 60, 120, 240, and 300 minutes following initial dose and next three dose increases, and one sample each at Weeks 1, 4, and 8.*

capacity to aid in the design of pivotal clinical studies. As such, no formal power calculations were performed by the sponsor.

Multiplicity. There was no adjustment for multiplicity.

Interim analyses. There was no interim analysis.

Statistical analysis. The primary efficacy endpoint was analyzed using an ITT group consisting of all randomized patients. All other efficacy analyses were conducted on available (nonmissing) data for the ITT group. Safety analyses were conducted on all randomized patients.

The distance walked analyzed by nonparametric and parametric methods. The nonparametric analysis was the primary analysis and used extended Cochran-Mantel-Haenszel (CMH) test. The secondary, parametric analysis used ANCOVA with terms for treatment group and center with baseline distance walked as covariates. Both parametric and nonparametric analyses utilized imputed values or ranks in the event that a patient had no Week-8 exercise test result or the Week 8 exercise test result was invalid. The rules for imputing values or ranks are shown in Table 27.

Table 27. Rules for imputing distance in 6-minute walk (P01:03)[42]

Event	Primary procedure for nonparametric analysis	Imputed values for parametric analysis
Death within 8 weeks; excluding transplantation and accidents	Lowest standardized rank of zero	0 m
Clinical decompensation within 8 weeks; excluding transplantation and accidents	Lowest standardized rank of zero	0 m
Transplantation	Lowest standardized rank of zero	0 m
Accident unrelated to disease or study	Last standardized rank carried forward	LOCF[43]
Adverse event (Survivor, Week 8)	Last standardized rank carried forward	LOCF
Lost to follow-up (Survivor, Week 8)	Last standardized rank carried forward	LOCF
Consent withdrawn (Survivor, Week 8)	Last standardized rank carried forward	LOCF

Other efficacy measures were defined and analyzed as follows. Statistical tests comparing these outcomes between treatment groups were added to the statistical methods after the final analysis plan was completed and after the database was unblinded.

Week 1 and Week 4 exercise capacity. The distances walked during exercise tests at 1 and 4 weeks were summarized and analyzed as secondary efficacy parameters. The methods used at Week 8 were applied to Weeks 1 and 4.

Borg Dyspnea score. The Borg Dyspnea Score, recorded at the time of exercise testing, was summarized descriptively, by treatment group, at Baseline, Week 1, Week 4, and Week 8. Treatment group differences in the change from Baseline were assessed using the Wilcoxon rank sum test.

Dyspnea-Fatigue Rating total score. The Dyspnea-Fatigue Rating Total Score was defined as the sum of scores for the three components: magnitude of task, magnitude of pace, and functional impairment. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test.

PPH Signs and Symptoms. The total PPH Signs and Symptoms Score was defined as the number of symptoms present out of those queried at a visit. In order to assess

[42] *Data from NDA 210272, study report for P01:03, table 9.7.*

[43] *Last observation carried forward.*

overall change from baseline to follow-up in the signs and symptoms of PPH, a "-1" was assigned for each sign and symptom present at the follow-up assessment and absent at baseline, a "+1" was assigned for each sign and symptom absent at the follow-up assessment but present at baseline, and a "0" was assigned otherwise. The overall change score from baseline to follow-up was calculated by summing these values over all signs and symptoms. All 16 signs and symptoms had to be assessed at both baseline and follow-up in order for the change score to be calculated. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test.

Hemodynamic measurements. Each hemodynamic parameter was summarized descriptively, along with change from Baseline and Week 8. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test. The hemodynamic parameters summarized included the parameters recorded directly on the CRF as well as the derived parameters CI, PVR, PVRI , SVR, SVRI , TPR, SV, and SI.

Subgroup analyses. With the small number of patients included in this study, no subgroup analyses were planned.

Pharmacokinetics. The plasma UT-15 concentration profile would be examined for achievement of steady state. The relationship between UT-15 concentration immediately prior to dose escalation (pseudo-steady-state concentrations) and UT-15 dose was to be examined. Apparent plasma clearance was to be determined for each infusion rate from each steady state concentration. Pharmacokinetic linearity was to be investigated based on individual plots of steady state concentration versus UT-15 doses. Attempts were to be made to correlate selected hemodynamic parameters (PVRI, CI, PAPm, RAPm, SAPm SI, HR and S_vO_2) and changes in these parameters with steady-state plasma UT-15 concentrations

A.3.4 Results

A.3.4.1 Subject demographics & baseline characteristics

The demographic and clinical background data for the 93 subjects enrolled in P01:03 are summarized in Table 28 below. Overall, the demographics were relatively balanced. The placebo population had been diagnosed with primary pulmonary hypertension (PPH) for a relatively short period of time (0.9 years) compared with the group that received UT-15 (3.1 years). The majority of patients were receiving digoxin and warfarin at baseline and around 40% were on lasix (see table 14.1.9.1 for details).

Table 28. Demographics (P01:03)[44]

	Placebo N=9	**UT-15 N=17**
Age mean±sd	37±15	37.5±19
Range	13-55	12-73
Gender Male (%)	7 (78)	14 (82)
Race Caucasian n (%)	7 (78)	17 (100)
Black	0	0
Hispanic, other	2 (22)	0
NYHA Class III n (%)	9 (100)	16 (94)
Class IV	0	1 (6)
Blood pressure mean±sd	117±17 / 81±8	111±14 / 75±10

[44] *Data from NDA 21-272, volume 2.24, table 14.1.5.*

Table 29. Complications of PPH at baseline (P01:03)[45]

	Placebo N=9	UT-15 N=17		Placebo N=9	UT-15 N=17
Cough	2 (22%)	5 (29%)	Hypoxia	0 (0%)	2 (12%)
Cyanosis	2 (22%)	2 (12%)	'Low cardiac output'	2 (22%)	4 (24%)
Dizziness	5 (56%)	12 (77%)	Orthopnea	3 (33%)	3 (18%)
Dyspnea on exertion	9 (100%)	17 (100%)	Peripheral edema	4 (44%)	4 (23%)
Edema	4 (44%)	5 (29%)	Right heart failure	1 (11%)	2 (12%)
Fatigue	6 (67%)	13 (76%)			

A.3.4.2 Disposition of subjects

Subject selection. No information is available about subject selection in protocol P01:03.

Protocol violations & deviations. There were two types of relevant protocol violations. Six patients were able to walk further than allowed per protocol on the six-minute walk (4 UT-15, 2 placebo). Additionally, because the some of the first five patients treated (UT-15, 02001, 02004, 03001, Placebo, 02002, 02003) tolerated UT-15 less well than anticipated, the DSMB requested an unblinding of these individuals. This unblinding was discussed with the FDA.

The remainder of the reported protocol violations were minor (see Clinical study report, section 10.2 for details).

Concomitant therapies. A majority of the subjects in both groups were taking anticoagulants, vasodilators, diuretics and digoxin during the trial, with no relevant differences in their use between treatment groups (see NDA vol. 2.24, table 14.2.7.3 for details). About 35% of both groups received oxygen during the study.

A.3.4.3 Six-minute walk

While all of the patients attempted the six-minute walk at baseline, 2 patients in the UT-15 group and 1 in the placebo group did not complete it. Table 30 summarizes the distances walked, counting only those patients with available data. There was a favorable numerical trend in distance walked for the UT-15 group evident by week 4. In analyses not shown, none of the differences approached nominal statistical significance of p=0.05.

Table 30. Distances (m; mean±sd) on 6-minute walk, actual and LOCF (P01:03)

	Actual distance[46]				Distance by LOCF[47]			
	Distance		Change		Distance		Change	
	Placebo N=9	UT-15 N=13-17	Placebo N=9	UT-15 N=13-17	Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17
Baseline	384±82	373±103	—	—	384±82	373±103	—	—
Week 1	396±82	420±97	+12±46	+25±101	396±82	393±107	+12±46	+19±88
Week 4	395±120	414±91	+10±70	+41±90	395±120	401±93	+10.3±70	+27±95
Week 8	379±111	422±96	-6±83	+39±72	379±111	410±95	-5.8±83	+37±68

Similar results were seen when the last-observation carried forward analysis was performed, although the differences did not achieve nominal significance of <0.05.

[45] *Data from NDA 21-272, volume 2.24, table 14.1.6.*

[46] *Data from NDA vol. 2.24, table 14.2.2.1*

[47] *Data from NDA vol. 2.24, table 14.2.2.1*

A.3.4.4 Hemodynamic changes

Invasive monitoring of several hemodynamic parameters and measurement of vital signs were performed at baseline, 1, 4, and 8 weeks. The results from selected relevant hemodynamic measures are shown below. Trends in favor of UT-15 on cardiac index (increased) and pulmonary vascular resistance (decreased) were reported for the UT-15 group.

Table 31. Hemodynamic assessments (P01:03)

		Value		Mean change		Median change	
		Placebo N=9	**UT-15 N=17**	**Placebo N=9**	**UT-15 N=17**	**Placebo N=9**	**UT-15 N=17**
Heart rate[48], bpm	Baseline Week 8	85±21 82±21	77±10 84±17	—	—	-3±6	+7±16
Cardiac index[49]	Baseline Week 8	2.43±0.6 2.40±1.0	2.32±0.9 2.73±1.0	-0.03±0.6	+0.42±0.6	-0.20	+0.36
Mean right atrial pressure[50], mmHg	Baseline Week 8	10.0±4 8.2±3.7	9.4±6 8.1±5.6	-1.8±3.6	-0.5±3.7	-1.0	-1.0
Mean pulmonary artery pressure[51], mmHg	Baseline Week 8	64±18 62±18	59±16 59±13	-2±3.6	0±12	—	—
Pulmonary vascular resistance[52], mmHg/L/min	Baseline Week 8	15.7±8 15.9±8	14.3±7 11.4±4	+0.2±3	-3.1±4[53]	+0	-2.6
Systemic vascular resistance[54], mmHg/L/min	Baseline Week 8	22.4±7 22.3±7	21.2±8 18.6±6	0±5	-3.2±5	+1.0	-2.7

In results not shown, no trends towards differences between the treatment groups were seen for the respiratory rate or mixed venous saturation.

A.3.4.5 Signs and symptoms of heart failure

The sponsor measured changes in the signs and symptoms of heart failure using three separate instruments. These scales are explained in Appendix One, where the reader is referred for details.

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[48] *Data from NDA vol. 2.24, table 14.2.3.1.*

[49] *Data from NDA vol. 2.24, table 14.2.3.2.*

[50] *Data from NDA vol. 2.24, table 14.2.3.6.*

[51] *Data from NDA vol. 2.24, table 14.2.3.9.*

[52] *Data from NDA vol. 2.24, table 14.2.3.10.*

[53] *P-value =0.027 per sponsor's comparison of group distributions from Wilcoxon rank sum.*

[54] *Data from NDA vol. 2.24, table 14.2.3.18.*

Table 32. Signs and symptoms of heart failure (P01:03)

		Value		Mean change		Median change	
		Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17
Borg dyspnea score[55]	Baseline Week 8	2.4±2 3.4±2.5	3.2±1.3 3.1±1.8	+1.0±2.5	0±1.6	+1.0	0
Fatigue-dyspnea rating[56]	Baseline Week 8	6.3±1.9 5.8±1.6	6.3±1.5 7.1±1.5	-0.25±1.4	+0.57±1.3	0	0
PPH signs and symptoms[57]	Baseline Week 8	8.2±3 8.2±2	7.9±2 6.7±1.9	0±1.7	-1.1±1.5	0	-1

A.3.4.6 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown in Table 17.

Table 33. Disposition of subjects (P01:03)[58]

Event	Placebo N=9	UT-15 N=17
Any adverse event	8 (89%)	17 (100%)
Serious adverse event	1 (11%)	4 (24%)
Discontinued with adverse event	0	2 (12%)
Deaths	0	0

A.3.4.6.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.3.4.6.2 Comments on specific safety parameters

Deaths. There were no deaths during the trial.

Serious adverse events. Table 34 below summarizes the SAEs reported in the trial.

Table 34. Serious adverse events (P01:03)[59]

	Subject	Event	Dose	Day of onset
Placebo	02013	Vasovagal reaction	2.5	2
UT-15	02001	Systemic hypotension[60]	5.0	2
	02005	Exacerbation of pulmonary hypertension	2.5	53
	02009	Bradycardia and hypotension, vasovagal[61]	0	2
		Syncope	5.0	28
		Pleural effusion	5.0	41
	03006	Ruptured ovarian cyst	15.0	26

[55] *Data from NDA vol. 2.24, table 14.2.4.*

[56] *Data from NDA vol. 2.24, table 14.2.5.*

[57] *Data from NDA vol. 2.24, table 14.2.4.*

[58] *Data from NDA 21-272, vol. 2.24, table 12.2.1.*

[59] *Data from NDA vol. 2.24, table 12.3.1.2.*

[60] *Occurred during a decrease in UT-15 infusion.*

[61] *Occurred during baseline catheterization, before study drug was commenced.*

Adverse events. Table 35 below summarizes the reported adverse events in the trial, emphasizing the prominent occurrence of infusion site pain in the patients who received UT-15.

Table 35. Subjects with adverse events (P01:03).[62]

	Placebo N=9	UT-15 N=17		Placebo N=9	UT-15 N=17
Infusion site reaction	2 (22%)	16 (94%)	Infusion site bleed/bruise	2 (22%)	5 (29%)
Infusion site pain	2 (22%)	15 (88%)	Abdominal pain	1 (11%)	4 (24%)
Headache	4 (44%)	14 (82%)	Anorexia	0 (0%)	4 (24%)
Diarrhea	1 (11%)	10 (59%)	Hypotension	0 (0%)	4 (24%)
Nausea	1 (11%)	10 (59%)	Vomiting	0 (0%)	4 (24%)
Vasodilatation	1 (11%)	8 (47%)	Insomnia	3 (33%)	1 (6%)
Jaw pain	1 (11%)	7 (41%)	Syncope	3 (33%)	1 (6%)
Pain	0 (0%)	7 (41%)			

Discontinuations. There were two discontinuations in the UT-15 group. Patient 02001 was discontinued on day 3 for chest pressure and hypotension. Patient 03007 discontinued on day 40 due to site pain.

Effects on vital signs. During initiation of UT-15 and at every dose adjustment the sponsor collected blood pressure data for 8 hours (NDA vol. 2.24, table 14.3.7). At every increase in dose there was a small decrease in systolic and diastolic BP within the first 8 hours of approximately 4 to 8 mmHg in both the UT-15 and placebo groups. There were no consistent changes in the pulse rate.

Effects on ECG. Changes in QT interval were assessed at baseline, 8 weeks and at last follow-up. After 8 weeks on UT-15, the QT interval decreased by a mean of 9.6 msecs, compared with an increase of 10 msecs for the patients who received placebo. At last follow-up, the mean QT decreased 0.3 msecs in UT-15 and 4 msecs in placebo (NDA vol. 2.24, table 14.3.6). No significant differences in mean changes in the QRS axis or PR interval were measured.

A.3.5 Summary

A.3.5.1 Efficacy summary

Study PO1:03 enrolled small numbers of patients with pulmonary hypertension in a randomized, double-blind fashion to receive either UT-15 or placebo. Overall, while not powered to detect significant clinical effect, the trial did find several trends in support of a clinical and a hemodynamic effect of UT-15 in patients with pulmonary hypertension.

Hemodynamic effects

- A decrease in pulmonary vascular resistance and an increase in cardiac index of 15-20% between baseline and week 8 was observed in patients who underwent invasive monitoring.
- An increase in the mean heart rate was observed of approximately 10 beats per minute between baseline and week 8 (placebo-subtracted).

Clinical effects

- There was a favorable numerical trend in mean distance walked in six minutes for the UT-15 group evident by week 4, amounting to 45 meters (placebo-subtracted).

[62] *Data from NDA vol. 2.24, table 12.2.2.*

No difference in distance walked was evident at the end of week one. This trend was evident in the population with available data as well as the LOCF analysis.

- The sponsor used three scales assessing changes in the signs and symptoms of heart failure. For each of these (Borg Dyspnea Scale, Dyspnea-Fatigue Index, and Signs and Symptoms of PPH) the trends were in favor of the UT-15 group. The numerical changes did not achieve nominal statistical significance in any of the three areas.

A.3.5.2 Safety summary

See the Integrated Review of Safety. The current trial enrolled 26 patients, limiting the available safety exposure. Of note:

- Pain at the site of infusion was nearly universal in the group receiving UT-15, but required drug discontinuation in only one of the 16 patients in the UT-15 group.
- A number of other adverse events were substantially more common in the UT-15 group than in the placebo group: headache, nausea, diarrhea, and jaw pain.
- Over the course of 8 hours, no consistent effects on heart rate, blood pressure or on any ECG parameter (including QT) were seen in the trial for UT-15, when compared with placebo.

A.3.5.3 Reviewer's conclusions

Study P01:03 examined the effect of UT-15 in a population with moderately-advanced heart failure related to primary pulmonary hypertension (PPH). It was a double-blind study, and the sponsor made reasonable efforts to blind the assessors to the treatment. Almost all of the patients taking UT-15 experienced site pain, limiting the possibility for true blinding, an apparently unavoidable consequence of the drug's use. For the primary endpoint (6-minute walk distance), the use of UT-15 was associated with an increase in the mean distance walked of around 45 meters. In addition, this study provided data that support, but do not demonstrate, an effect of UT-15 on the hemodynamics and symptoms of heart failure related to pulmonary hypertension.

This trial enrolled few patients and was necessarily limited in its power to detect significant effects of UT-15, but was a blinded comparison with placebo. It also enrolled only patients with Primary Pulmonary Hypertension (PPH), in distinction to the other blinded clinical trials that enrolled patients with pulmonary hypertension due to both primary and secondary causes. Data from the trial support, but do not demonstrate, an effect on clinically-relevant measures of heart failure due to pulmonary hypertension (6-minute walk distance, signs and symptoms of CHF) as well as changes in hemodynamics consistent with a salutary effect of UT-15. The primary finding from the safety was the nearly universal occurrence of site pain following the use of UT-15.

A.4 Studies P01:04, P01:05: An international multicenter, double-blind, randomized, parallel placebo-controlled comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with pulmonary hypertension: a 12-week study.

A.4.1 Sites and investigators

The two studies were run concurrently. There was overlap in study investigators/sites for the two protocols. Many investigators that enrolled subjects in study P01:04 also enrolled subjects in Study P01:05. Those who enrolled subjects into study P01:04 were all North American Sites (includes Canada and Mexico). There were additional 16 sites all outside of North America for which subjects were enrolled into study P01:05. The individual investigators and sites as well as the number enrolled in P01:04 and P01:05 are shown in Table 36.

Table 36. Sites and investigators (P01:04-05)

Site	Investigator	Location	N	
			:04	:05
01	Sean Gaine MD	University of Maryland,Baltimore, MD	1	0
02	Robyn Barst, MD	Columbia Presbyterian ,New York, NY	22	1
03	Stuart Rich, MD	Rush Presbyterian-St. Lukes Med Center, Chicago, IL	18	3
04	Ronald Oudiz, MD	Harbor-UCLA Medical Center, Torrance, CA	19	5
05	Michael McGoon, MD	Mayo Clinic, Rochester, MN	12	2
06	David Badesch	Univ of Colorado Health Science Center, Denver, CO	3	0
07	Ivan Robbins	Vanderbilt University Medical Center, Nashville, TN	10	3
08	Victor Taspon	Duke University Medical Center, Durham, NC	10	1
09	Adaani Frost. MD	Baylor Coll of Medicine and Methodist Hosp, Houston, TX	19	3
10	Robert Bourge, MD	University of Alabama, Birmingham, AL	27	8
11	Ramona, Doyle, MD	Stanford University Medical Center, Stanford, CA	3	1
12	Theresa DeMarco, MD	University of California Moffitt Hosp, San Francisco, CA	7	3
13	Joel Wirth, MD	Maine Medical Center, Portland, ME	2	0
14	Richard Channick, MD	Univ of Calif at San Diego Medical Center, San Diego, CA	13	1
15	Gregory Elliott, MD	Latter Day Saints Hospital, Salt Lake City, UT	8	1
16	Srinivas Murali, MD	University of Pittsburgh Medical Center, Pittsburgh, PA	10	2
17	David Langelben, MD	Jewish General Hospital, Montreal Quebec, Canada	7	2
18	David Ostrow, MD	Vancouver Gen Hosp, Vancouver, BC, Canada	1	1
19	Robert Schilz. MD	The Cleveland Clinic, Cleveland, OH	8	4
20	Julio Sandoval	Instituto Nacional de Cardiologia, Mexico City, Mexico	10	5
21	Nicholas Hill, MD	Rhode Island Hospital, Providence, RI	4	2
22	Ben deBoisblanc, MD	Louisiana State Univ Medical Center, New Orleans, LA	7	5
23	Dunbar Ivy, MD	Children's Hospital, Denver, CO	3	0
24	Shelley Shapiro	University of Southern California, Los Angeles, CA	0	6
50	Anne Keogh, MD	St Vincent's Hospital, Sidney NSW, Australia	0	24
51	Meinhard Knuessl,MD	Allgemeines Krankenhaus, Wein, Austria	0	7
52	Marion Delcroix, MD	University Hospital, Brussels, Belgium	0	9
53	Robert Naeije, MD	Free University of Brussels, Brussels, Belgium	0	22
54	Gerald Simmonneau, MD	Hospital Antioine Beclere, Clamart, France	0	28
55	Marius Hoeper, MD	Medical School of Hanover, Hanover. Germany	0	5
56	Neville Berkman, MD	Hadassah Ein Kerem Medical Center, Jerusalem, Israel	0	2
57	Isaschar Ben-Dov, MD	The Chaim Sheba Medical Center, Tel-Hashomer, Israel	0	8
58	Mordechai Kramer, MD	Rabin Medical Center, Petach Tikvah, Israel	0	10
59	Nazzareno Gaile, MD	University of Bologna, Bologna, Italy	0	15
60	Adam Tobicki, MD	National Tuberculosis Research Center, Warsaw, Poland	0	15
61	Miguel Gomez-Sanchez, MD	Hospital 12 de Octubre, Madrid, Spain	0	12
62	Carol Black, MD	Royal Free Hospital, London, UK	0	0
64	Tim Higgenbottam, MD	Sheffield University, Sheffield, UK	0	5
65	Andrew Peacock, MD	West Glasgow Hospitals, Glasgow, UK	0	15
66	Paul Corris, MD	Freeman Hospital, Newcastle Upon Tyne, UK	0	10

A.4.2 Background

Table 37. Dates (P01:04-05)

	P01:04	P01:05		P01:04	P01:05
Initial protocol	5/7/98	5/798	Last subject complete	12/2/99	2/3/00
Amendment 1	9/5/98	9/5/98	Original Analysis Plan	11/9/99	
Amendment 2	11/9/98	11/9/98	Analysis Plan Submitted	3/6/00	
Amendment 3	12/22/98	12/22/98	Analysis Plan Amended	3/23/00	
First subjects randomized	11/12/98	12/15/98	Unblinded	3/24/00	

The sponsor proposed to perform protocols P01:04 and P01:05 concurrently. The description in this review reflects the incorporation of all protocol amendments. As seen from the pivotal dates of the study, all amendments were dated prior to the completion of the initial subject's 12-week assessment. . The specifics of each amendment, therefore, will not be summarized in this review.

A.4.3 Study design

The timing of the procedures is shown in Table 38.

Table 38. Procedures (P01:04-05)

	Screen	Baseline		Treatment			
Week				1[63]	6[64]	12[65]	
Day		1[66]	2	9	44	87	88
Informed consent, medical history, physical exam	X						
Inclusion/exclusion criteria	X		X[67]				
Global Quality of Life, PHT Signs and Symptoms		X		X	X	X	
12-Lead ECG/chemistry/hematology		X				X	
Exercise capacity		X[68]	X[69]	X	X	X	
Swan-Ganz catheterization/hemodynamics			X				X
Randomization			X[70]				
Monitor: ECG/vital signs/TCO_2			X				
Pharmacokinetic samples[71]			X	X	X	X	
Infusion of study drug/evaluation of infusion site		X	X	X	X	X	X
Concomitant medication/AE reports	X	X	X	X	X	X	X

A.4.3.1 Number of subjects/ randomization

Four hundred seventy [470] with pulmonary hypertension with diverse etiologies were randomized.

A.4.3.2 Inclusion/ exclusion criteria

Inclusion criteria. Subjects were eligible to enroll if they were mentally and physically competent to administer study drug by the subcutaneous route. They could be of either gender between the ages of 8-75 years. These subjects were to have a diagnosis of pre-capillary pulmonary hypertension that could be a consequence of any of the following:

- Primary disease (primary pulmonary hypertension).
- Pulmonary hypertension secondary to connective tissue disease e.g. systemic sclerosis (scleroderma), limited scleroderma, mixed connective tissue disease, systemic lupus erythematosus, or overlap syndrome

[63] *±2 days*

[64] *±5 days*

[65] *±7 days*

[66] *May be conducted up to one week prior to enrollment.*

[67] *Includes hemodynamic criteria.*

[68] *Within 6 weeks of enrollment.*

[69] *Before catheterization.*

[70] *Within 48 hours of hemodynamic eligibility.*

[71] *Blood samples to be drawn between 9am- noon.*

- Pulmonary hypertension with congenital systemic left-right shunts (repaired or unrepaired).

Catheterization results at baseline had to demonstrate an increase in pulmonary pressures with normal left-sided function as defined by the following measurements:

- PAPm $\geq$ 25 mm Hg (at rest)
- PCWP (or left ventricular end diastolic pressure) $\leq$ 15 mm Hg
- PVR > 3 mm Hg

An echocardiogram performed within 3 months of enrollment had to demonstrate evidence of right sided dysfunction (dilatation or hypertrophy), with no evidence of left sided dysfunction and a the absence of mitral valve stenosis.

Other causes of CHF were to be excluded prior to enrollment. A chest X-ray was to exclude primary pulmonary alveolar disease, or severe interstitial disease. Thromboembolic disease was to be excluded by a ventilation/perfusion scan. If the scan was read as indeterminate or suggested a high probability of embolic disease then thromboembolic disease was excluded by either a pulmonary angiogram or spiral/helical/ultrafast computed tomography.

Subjects were to be optimally treated for pulmonary hypertension with stable medication for at least one month prior to baseline measurements. For those treated with corticosteroids stable doses of $\leq$ 20 mg/day of prednisone (or equivalent) for at least one month were required prior to enrollment. For those who such treatment was not contraindicated, anticoagulation with either warfarin (to an INR of between 1.5 and 2.5) or heparin to produce an aPTT between 1.3-1.5 times control was recommended. Higher levels of anticoagulation would be acceptable if clinically warranted. Despite the optimization of treatment, these subjects had symptom limited CHF (NYHA > II).

Comment. The population enrolled into this study differed from the population that was enrolled in the studies that led to the approval of Flolan. Only subjects with primary pulmonary hypertension were enrolled in the studies pivotal for Flolan approval. In the studies for UT-15 subjects whose pulmonary hypertension was secondary to either collagen vascular disease or left to right cardiac flow shunts also were recruited for enrollment.

In addition, the population with primary pulmonary hypertension in this study may contain the same or a different proportion of subjects whose pulmonary hypertension is a consequence of anorexogenic drug treatment. In contrast to other forms of pulmonary hypertension, those previously taking anorexogenic drugs have the stimulus of disease removed, i.e. the anorexogenic drug has been stopped. Those with their primary pulmonary hypertension as well as whose pulmonary hypertension is secondary to collagen vascular disease have ongoing disease processes.]

Exclusion criteria. Subjects were excluded if they were pregnant or nursing (women); if they had any new therapy or experimental therapy added or withdrawn within the last month; or if they were treated within the last month with approved or experimental prostaglandin analogues by any route of administration. Anticoagulants could be discontinued up to one month prior to enrollment.

Subjects were excluded if they had evidence of parenchymal lung disease based on the results of pulmonary function test that demonstrated:

- Total lung capacity $\leq$70% of predicted.
- If TLC was between 70-80%, then a high resolution CT which demonstrated diffuse interstitial fibrosis or alveolitis.

- FEV1/FVC ≤50%
- A Diffusion Lung Capacity (D_{LCO}) <50%

Subjects were also excluded if they had pulmonary hypertension associated with: HIV infection, portal hypertension, uncontrolled sleep apnea, sickle cell disease, schistosomiasis, recent (within 3 months) use of prescription appetite suppressants, or left sided heart disease (aortic or mitral valve disease); constrictive pericardial disease, congestive or restrictive cardiomyopathy, uncontrolled blood pressure (SBP >160 or DBP >100 mm Hg) or evidence of left sided disease (a PCWP >15 mm Hg; left sided EF <40%; left ventricular shortening fraction <22% by echocardiography), or cardiac ischemia.

Subjects who were incapable of exercise because of a musculoskeletal disorder or who required a machine that precluded free ambulation were excluded from the study.

Subjects were excluded if the baseline 6-minute exercise distance was outside the boundaries of 50-450 meters.

A.4.3.3 Formulation

A formulation at a concentration of 1.0 mg/ml of UT-15 was utilized for active drug infusion rates of ≤22.5 ng/kg/min.

A formulation at a concentration of 2.5 mg/ml of UT-15 was utilized for active drug at a doses of >22.5 ng/kg/min

A corresponding reference vehicle[72] was used:

Table 39. Formulations (P01:04-05)

	Vehicle	1.0 mg/ml	2.5 mg/ml
UT-15	0.0	1.0	2.5
Sodium citrate, dihydrate	5.0	6.3	6.3
Metacresol	3.0	3.0	3.0
Sodium chloride	5.0	5.3	5.3
Citric acid	1.8	-	-
Sodium Hydroxide	1.08	0.24	0.32
Lot (P01:04)	800348	800412, 800504, 800506,800557, 800559	800413, 800505, 800560
Lot (P01:05)	800001, 800348, 800860	800412, 800504, 800506,800557, 800755, 801013	800413, 800505, 800558, 800756

Comment. There appears to be an asymmetry in the vehicle formulation. There are two concentrations for active drug and only one for vehicle. Apparently each subject was allocated two bottles with different concentrations of drug/vehicle so that the appropriate dose could be formulated for infusion. For the UT-15 group these two concentrations differed, for the vehicle subjects the concentration was the same. Thus, symmetry was maintained and the study adequately blinded.

A.4.3.4 Dosage/ administration

Criteria for infusion pump. The following are the prespecified criteria for the infusion pump:

- Portable: small size and lightweight.

[72] *This review will refer to the placebo as a vehicle.*

- Infusion rate increments: sufficient to adjust the dose by 0. 4 ug/min or approximately 0.002 mL/hr.
- Alarms: occlusion, end of infusion, low battery, clogged or obstructed infusion set, motor malfunction or programming error.
- Accuracy of delivery: ±6% or better, with equivalent delivery units.
- Type of action; positive pressure.
- Reservoir composition; polyvinyl chloride, polypropylene or glass.

Specific pumps listed by the sponsor include: MiniMed MMT #506, 507 and 507c.

Administration. The formulation was to be administered subcutaneously. The site of infusion was almost invariably abdominal. The catheter was to be changed at least every third day and a new catheter inserted in a different site. Initially, while in hospital, the catheter was changed daily.

A.4.3.5 Randomization and blinding

Randomization. Subjects were randomized in a 1: 1 ratio to vehicle or UT-15. The randomization process was handled at a central location. Randomization was stratified based on three parameters.

- The etiology of disease (primary pulmonary hypertension versus other causes of pulmonary hypertension).
- Six-minute exercise distance (low =50-150 meters, versus high 151-450 m).
- Subjects with pre-capillary hypertension due non-primary causes were also stratified by the use of vasodilator use at baseline.

Within each stratum the stratification was for block sizes of 2.

The initial randomization was intended to include stratification based on study i.e. P01:04 or P01:05 . The initial randomization, however, was inadvertently performed across both studies. On 16 June 99, 238 subjects were already randomized without stratification based on the particular study, the randomization process was amended to include study number as a strata.

Blinding. Amber ampoules were used so blinding of cream colored in the ampoule would not indicate the specific treatment.

The study was double blinded (triple blinded? i.e. sponsor). In addition, during the 12-week exercise portion of the study, for each study site, an independent exercise administrator other than the physician who cared for the subject, administered the exercise test. This administrator was not otherwise involved in the subject's care. The results of the exercise test were not to be made available to other study personnel until both studies were completed at all centers and the database secured.

The blinding, however was not perfect.

- It is clear that the subject was not blinded to their exercise results and consequently, the information may have gotten to the investigator (there is really no way to get around this).
- Subjects were unblinded at the end of the 12-week exercise test to facilitate crossover to open-label treatment. It is unclear to what extent the subjects data was locked in prior to the unblinding of each individual.
- Subjects could also be unblinded if there was a safety issue and that unblinding was pivotal to the subject's care.

- The very nature of the infusion may unblind the treatment.

A.4.3.6 Oversight

Based on amendment #2, a steering committee that was to consist of up to six clinicians who were investigators in the clinical trial as well as one sponsor's representative and one statistician. The steering committee was to guide the study. This committee was to meet at least once when 50% of those enrolled completed the study, to perform an interim analysis for efficacy on the pooled data. The analysis was to be unblinded as to treatment. Amendment #3, however, modified the protocol so that no interim efficacy analysis was performed.

There was a data safety monitoring board (DSMB) that consisted of one statistician as well as up to two clinicians not involved the study. Three interim safety looks were performed, after 20%, after 40% and after 60% of the subjects completed the 12-week period. The committee received and reviewed masked tabulations of serious adverse events and deaths from pooled treatment groups. P-values were supplied and screened for lower rates in the vehicle group. If the p-value favors the vehicle group ($p<0.25$) and if requested, the DSMB would be supplied masked tabulations by treatment group. Unmasked data could be supplied to the DSMB. Under certain circumstances, the DSMB could request efficacy data. Should the DSMB request the efficacy data, a p-value of <0.0001 would be required to terminate the study. (It seems that some one had the ability to construct this data and therefore, had the ability to unblind the study).

A.4.3.7 Duration/ adjustment of therapy

Study drug was initiated after exercise and hemodynamic measurements on Day 2 of the protocol (see table 1.7 for a list and timing of procedures). The initial dose of UT-15 or corresponding vehicle was 1.25 ng/kg/min. This dose was the maximum allowed at the end of week one. If the infusion was not tolerated, the dose could be decreased to a tolerated infusion rate. The initial dosing was to take place in the clinic. Dosing adjustments should, but did not necessarily have to be performed in the clinic.

At the end of week 1 the dose could be increased at rates no greater than 1.25 ng/kg/min till week 4. At week 4, the dose could be increased by rates of 2.5 ng/kg/min. The maximum doses at each week are shown in Table 40.

Table 40. Maximum doses (ng/kg/min) allowed during various weeks of the study (P01:04-05)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Days	2-9	10-16	17-23	24-30	31-37	38-44	45-51	52-58	59-65	66-72	73-79	80-88
Dose	1.25	2.5	3.75	5.0	7.5	10	12.5	15	17.5	20	22.5	22.5

Dose increases were warranted if:

- The subject's symptoms of pulmonary hypertension did not improve, or
- The subject's clinical condition deteriorated and the subject became increasingly symptomatic.

Dose reduction could be entertained based on the judgement of the investigator if there was evidence of:

- Excessive pharmacological action as judged by vital signs.
- Onset of adverse events such as headache, nausea, emesis, restlessness and anxiety.
- Onset of significant pain, or worsening of pain at the infusion site.

Large dose reductions or abrupt cessation of treatment was to be avoided.

Although catheterization was allowed for subject care, dosing modification was to be based on symptoms of pulmonary hypertension and not the outcome of catheterization.

A.4.3.8 Efficacy endpoints

Primary end point. The primary end point is the effect of UT-15 on exercise distance at week 12 of treatment. Each the individual studies as well as the pooled studies were specified for analysis. The planned analysis was an intent to treat, non-parametric covariance analysis (specifically, the sponsor will use a Cochran-Mantel-Haenszel mean score statistic). Covariates in this model were to include center, baseline exercise distance, vasodilator use at baseline, etiology of pulmonary hypertension (i.e. primary versus all other causes) and steroid therapies that were added during the 12-week observation period. For all inferential analyses, the level of significance will set to 0.05 with two sided-alternative hypothesis.

Subjects were removed from study without follow-up for the following reasons:

- Transplantation.
- Rescue with chronic >5 days intravenous Flolan.
- Rescue with chronic >5 days intravenous inotropic therapy.
- AE judged sufficiently serious to warrant discontinuation from the study.

When subjects did not complete the full 12-weeks of treatment for the following reason, death, clinical deterioration of sufficient intensity to be prematurely discontinued from the study, transplantation, accident unrelated to disease adverse event, lost to follow up or withdrawal of consent, values were imputed. The rules for imputation are shown in Table 41. Subjects who discontinued from the study were to be followed for 12-weeks. A 6-minute walk and symptom assessment was to be performed at 12-weeks. The data, however, from the last test while on study drug was to be used in any analysis. For the secondary end points (see below) subjects who prematurely discontinue were to be censored.

Table 41. Rules for imputation among those who had no 12-week measurements (P01:04-05)

Event	Primary procedure for non-parametric analyses	Imputation for parametric analyses	Secondary end-points
Death within 12 weeks Clinical decompensation[73] Transplantation	Lowest standardized rank	0-Meters	Censored
Accident (limits ambulation)	Last rank carried forward	LOCF[74]	Censored
Adverse event (survived)	Last rank carried forward	LOCF	Censored
Lost to follow-up (survived)	Last rank carried forward	LOCF	Censored
Consent withdrawn (survived)	Last rank carried forward	LOCF	Censored
Discontinued prior to week-1 measurement	Not stated	Not stated	Censored

Subjects were not to have medications added during the study unless it was a medical necessity. Since these medications could effect exercise distance, the following analyses were to be included.

- Subjects who began treatment with new pulmonary hypertension medications during the study were to be considered treatment failures. An alternative method was to rank subjects based on vasodilator use changes.

[73] *Received rescue therapy.*

[74] *Last observation carried forward.*

- Steroid or vasodilator treatment changes were not to be taken into account.
- Steroid therapy or therapies to treat pulmonary hypertension that were added during the 12-week observation period would be treated as a covariate.
- Steroid therapy or therapies to treat pulmonary hypertension were added during the 12-week period as a covariate.

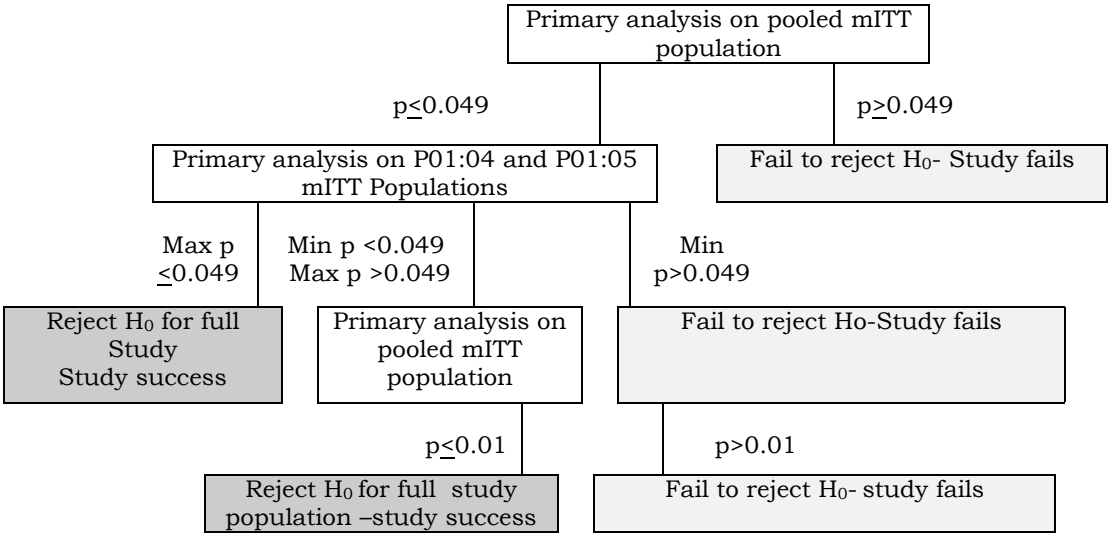
A parametric analysis of covariance was to be performed as a secondary analysis.

A secondary analysis of the primary endpoint is an ANCOVA, with the 6-minute distance walked at Week 12 to be imputed as a function of distance walked at baseline. Other covariates were to include center, etiology of pulmonary hypertension, vasodilator use and steroid therapy (or therapies) to treat pulmonary hypertension that were added during the 12-week observation period.

Additional analyses were to be performed where the last observation carried forward for each subject whether they deteriorated or were discontinued due to adverse events.

Rules by which the study was to be considered a success. The sponsor proposed to define the study as a success based on a hierarchical analysis. In essence the study would be considered a success either if both studies were successful (p <0.049) or either study demonstrated a p value of <0.049 and the overall pooled study showed a p-value of <0.01. The flow sheet for the sponsor's analysis is shown in Figure 10[75].

Figure 10. Flow for demonstrating success (P01:04-05)



Secondary end points. Secondary reinforcing measures of efficacy are as follows:

- Signs and symptoms (see Table 42) as measured by (1) changes in frequency/severity and (2) time to a subject's discontinuation from study due to clinical deterioration, transplant secondary to deterioration (or lack of improvement) or death.

[75] *Derived from figure 8.1 p 6365-3200*

Table 42. Specific signs and symptoms (P01:04-05)[76]

Signs	Symptoms
Weight	Ascites
Blood pressure and pulse rate	Chest pain*
Loud P 2 sound*	Dizziness*
Right ventricular S3 sound* (third heart sound)	Dyspnea at rest*
Right ventricular S4 sound* (fourth heart sount)	Dyspnea on exertion*
Right ventricular heave*	Paroxysmal Nocturnal dyspnea*
Murmur of tricuspid insufficiency* (diastolic murmur)	Fatigue*
Murmur of pulmonic insufficiency * (systolic mumur)	Nausea/vomiting
Hepatomegaly*	Orthopnea*
Jugular venous distention at 45 degrees*	Palpitations*
Edema*	Syncope*
	Thirst

The above signs were rated as a change from baseline. If the sign or symptoms worsens (went from absent to present) a "–1" is assigned, for no change a "0" is assigned and for an improvement (i.e. present to absent) a "+ 1" is assigned. The overall score was assigned based on total # of changes in signs and symptoms, provided at least eight of the 16 signs and symptoms are assessed at both baseline and follow –up. The difference between treatment groups for the individual components is assessed using either a chi-square test (for dichotomous data) or Wilcoxon Rank Sum Test Statistic (for ordinal or continuous variable).

- The "Dyspnea Fatigue Index" evaluated signs and symptoms of pulmonary vascular disease. This index contains three criteria, each with potential values of 0-4 (Table 43). The change of the aggregate index between week 12 and baseline was the key analysis for this parameter. The difference between treatment groups is to be analyzed with a Wilcoxon Rank Sum Statistic. The index as completed by the treating physician (not exercise administrator) in conjunction with the subject's report of symptoms.

Table 43. Dyspnea Fatigue Index criteria (P01:04-05)

	Score	Criteria
Magnitude of task	4	Extraordinary- Symptomatic only with extraordinary activity (e.g. running, carrying heavy loads on level ground)
	3	Major- Becomes symptomatic only with major activities(e.g. climbing more than 3 flights of stairs, carrying a moderate or heavy load on level ground)
	2	Moderate- Becomes symptomatic with moderate or average tasks (e.g. walking up a gradual hill, climbing up less than three flights of stairs, carrying a light load on level ground
	1	Light- Becomes symptomatic with light activities (e.g. walking on level ground)
	0	None- Symptomatic at rest or lying down
Magnitude of pace	4	Extraordinary- All tasks carried out at a normal pace
	3	Major- Major tasks (see above) are performed at a reduced rate
	2	Moderate- Moderate tasks performed at a reduced rate
	1	Light- Light tasks are performed at a reduced rate
	0	None- Symptomatic at rest
Functional impairment	4	None- Can carry out usual activities and occupation
	3	Slight-Distinct impairment in at least one activity . No activities re completely abandoned
	2	Moderate-Changed jobs or abandoned at least one activity
	1	Severe-Unable to work or has given up most of usual activities
	0	Very Severe- unable to work and has given up most or all usual activities

[76] *These were listed in Appendix C of the study report. The CRF, however only collected 16 symptoms noted by an *. Dyspnea at rest, dyspnea on exertion, and paroxysmal nocturnal dyspnea were all assessed as 'dyspnea'.*

- Cardiopulmonary hemodynamic measurements consisted of: heart rate, SAPs, SAPd, SAPm, PAPs, PAPd, PAPm, RAPm, PCWPm, and CO.

Subjects will be catheterized for invasive hemodynamics (Swan Ganz). The time of placement of the catheter relative to measurements is not stated and not standardized. Serial measurements of hemodynamics for cardiac output and PAPm required that the three consecutive measurements must differ by less than or equal to 20% with individual measurements taken at least 10 minutes apart. The last value that defined the stable measurement was to be the value recorded on the CRF. For most subjects cardiac output was to be defined either by the thermal dilution or the Fick method. For those subjects with congenital shunts, however the Fick method was to be used. The differences between treatment groups will be analyzed by ANCOVA (i.e. parametric linear model)

- Mixed venous saturation, FiO_2 and systemic oxygen saturation (by pulse oximetry).
- Global Quality of Life Measurements at baseline and weeks 1, 6 and 12

The specifics of the "Living With Heart Failure" questionnaire[77] are shown below: The questionnaire was validated in 83 subjects with left ventricular dysfunction[78]. The metric has not been validated in subjects with pulmonary hypertension.

Did your heart failure prevent you from living as you wanted during the last month by

1. *Causing swelling in your ankles, legs etc.?*
2. *Making you sit or lie down to rest during the day?*
3 *Making your walking about or climbing stairs difficult?*
4 *Making your working around the house or yard difficult?*
5 *Making your going places away from home difficult?*
6 *Making your sleeping well at night difficult?*
7 *Making your sleeping to or doing things with your friends or family difficult?*
8 *Making your working to earn a living difficult?*
9 *Making your recreational pastimes, sports or hobbies difficult?*
10 *Making you sexual activities more difficult?*
11 *Making you eat less of the foods you like?*
12 *Making you short of breath?*
13 *Making you tired, fatigued, or low on energy?*

[77] *Copyright University of Minnesota 1986.*

[78] *Rector, TS; Kubo, SH and Cohn, JN; " Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire; Heart Failure, 1987; 198-209.*

> *14 Making you stay in a hospital?*
>
> *15 Costing you money for medical care?*
>
> *16 Giving you side effects from medications?*
>
> *17 Making you feel you are a burden to your family or friends?*
>
> *18 Making you feel a loss of self-control in your life?*
>
> *19 Making you worry?*
>
> *20 Making it difficult for you to concentrate or remember things?*
>
> *21 Making you feel depressed?*

The QOL questionnaire, per publication, consists of four dimensions:

- A global score (all questions),
- A physical dimension score (questions # 2-7, 12 and 13),
- Emotional dimension (questions 17-21), and
- Economic dimension.

- ***Borg Scale***. The exercise administrator, in conjunction with the exercise test, queried the subject as to the degree of shortness of breath (the Borg Scale) associated with the 6-minute walk. The subject was to be given the following set of instructions:

> *" I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you should chose from 0.5 to 2; if you were somewhat short of breath you should select 3 and if the breathing was very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represent the greatest shortness of breath that you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life choose a number greater than 10 that represents how short of breath you feel. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between."*

There was no prespecified method to incorporate the Borg Scale in assessing clinical improvement.

A.4.3.9 Pharmacokinetics

A population approach (NONMEM) was to be utilized in the pooled study data. The following covariates were employed: age; gender; ethnic background, use of concomitant calcium channel blockers, anticoagulants and diuretics, renal function (creatinine clearance).

No attempt was made to ascertain whether and to what extent metabolites are formed. There is some uncertainty if any metabolites are accumulated and whether they are active biologically (either as agonists or antagonists).

A.4.3.10 Statistical considerations

Sample size calculations. Based on the assumption of a 55 meter difference between UT-15 and Vehicle and a standard deviation of 110 meters, assuming an alpha of 0.05; a total of 105 subjects/group would have a 95% power to be successful.

Stratification. Subjects were to be randomized centrally and stratified based on type of pulmonary hypertension (primary versus secondary), exercise performance at baseline (low ≤150 meters or high >150 meters) and for those with secondary pulmonary hypertension, vasodilator use at baseline (yes versus no). There were therefore a total of 6 potential stratification groups. These are listed in Table 44. After the first 238 subjects were enrolled, stratification also included study.

Table 44. Stratification (P01:04-05)

Etiology	Baseline exercise	Vasodilator use
Primary	High	
Primary	Low	
Secondary	High	Yes
Secondary	High	No
Secondary	Low	Yes
Secondary	Low	No

Interim looks. There were no interim looks for efficacy. The proposed interim look during the second protocol amendment was subsequently dropped.

A.4.4 Results

A.4.4.1 Subject demographics & baseline characteristics

Specific baseline characteristics are shown below:

Table 45. Baseline characteristics (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh N=109	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Age, years	Mean	43.2	45.3	45.5	43.9	44.4	44.6
	±SE	±1.4	±1.4	±1.3	±1.3	±0.9	±1.0
Gender	F/M	95/16	96/17	90/35	101/19	185/51	197/36
	%F	[86%]	[85%]	[72%]	[84%]	[78%]	[85%]
Caucasian		86	91	112	107	198	198
Black		5	8	3	5	8	13
Asian		6	4	2	1	8	5
Hispanic		13	8	6	6	19	14
Other		1	2	2	1	3	3
Primary pulmonary hypertension		59	61	77	73	136	134
Collagen Vascular		30	25	19	16	49	41
Cardiac Shunts		22	27	29	31	51	58
NYHA Class (%)	II	16 (14)	10 (9)	12 (10)	15 (13)	28 (12)	25 (11)
	III	85 (77)	93 (82)	107 (86)	97 (81)	192 (81)	190 (82)
	IV	10 (9)	10 (9)	6 (5)	8 (7)	16 (7)	18 (8)
Duration at current NYHA, months	Mean	12.1	17.2	19.0	17.8	15.7	17.5
	±SE	±2.5	±2.9	±2.4	±2.1	±1.8	±1.8
Weight, Kg	Mean	73.8	73.3	72.1	67.6	72.9	70.4
	±SD	±19.9	±21.1	±16.3	±18.0	±18.1	±19.8
Height, cm	Mean	162.5	161.2	163.4	163.0	163.0	162.1
	±SD	±9.9	±10.5	±9.5	±8.5	±9.7	±9.6
BSA, m^2	Mean	1.8	1.8	1.8	1.7	1.8	1.7
	±SD	±0.2	±0.3	±0.2	±0.2	±0.2	±0.2
Pulse, bpm	Mean	82.4	83.5	81.8	82.1	82.1	82.8
	±SD	±12.6	±12.5	±12.7	±11.5	±12.6	±12.0
Systolic blood pressure, mmHg	Mean	117.3	116.7	116.3	115.5	116.8	116.1
	±SD	±16.9	±13.8	±16.3	±14.1	±16.6	±14.0
Diastolic blood pressure, mmHg	Mean	75.9	73.3	74.3	73.4	75.1	73.3
	±SD	±11.1	±12.0	±10.5	±11.5	±10.8	±11.7
Respiratory rate, min^{-1}	Mean	19.5	19.2	19.1	18.9	19.3	19.1
	±SD	±3.1	±2.8	±3.5	±3.9	±3.4	±3.4

The demographics were fairly well balanced across studies and across treatment groups. There were however, more males in the 01:05 vehicle group than in any other group. The vast majority of subjects were NYHA class III subjects (approximately 80%). The vast majority of those enrolled were also females approximately 85%). There proportion of subjects with primary pulmonary hypertension in the 01:05 study was greater than in the 01:04 study. The distribution of these subjects between UT-15 and vehicle were, however similar. There were a greater fraction of those enrolled in study P01:04 who had their pulmonary hypertension as a consequence of collagen vascular disease than in study P01:05.

Those with collagen vascular disease consisted of those with scleroderma (12-treatment, 13-vehicle), limited scleroderma (13-treatment, 7-vehicle); mixed connective tissue disease (8-treatment, 9-vehicle); systemic lupus erythematosis (7-treatment, 18-vehicle); and overlap syndromes (1-treatment; 2-vehicle). There were relatively more subjects in the vehicle group whose etiology of pulmonary hypertension was a consequence of SLE.

Those defined as having pulmonary hypertension as a consequence of primary disease probably consisted of those who had idiopathic pulmonary hypertension as well as whose disease was a consequence of anorexogenic drug use.

Comment. This reviewer does not know if the natural history of pulmonary hypertension as a consequence of anorexognic drug use as primary pulmonary hypertension are the same. For those with primary pulmonary hypertension secondary to anorexogenic use, the ongoing stimulus has been removed. The other causes in general (with the exception of repaired congenital shunts) do not have the inciting stimulus for pulmonary hypertension terminated.

The number of subjects in each cohort is shown in Table 50. There were very few subjects with low exercise capacity in the entire cohort.

A.4.4.2 Disposition of subjects

The flow of subjects through the study is shown in Table 46.

Table 46. Disposition of subjects (P01:04-05)

	P01:04		P01:05		Pooled	
	Vehicle	UT-15	Vehicle	UT-15	Vehicle	UT-15
Randomized	224		246		470	
Received treatment	224		245		469	
	111	113	125	120	236	233
Completed 12 weeks	104	96	117	104	221	200
Did not complete	7	17	8	16	15	33
Death	4	4	3	3	7	7
Deteriorated	2	1	4	5	6	6
Transplant	1	0	0	0	1	0
Adverse event	0	12	1	6[79]	1	18
Withdrew consent	0	0	0	2	0	2

A.4.4.3 Oversight Committees

In a supplement dated 3 November 2000, United Therapeutics submitted summaries of the DSMB meetings. The members of the committee were Drs. Brundage, Harrell, Churchill and Fishman. Reports are available for three meetings 20 July 1999; 18 October 1999, and 24 November 1999. After the second meeting the DSMB requested baseline hemodynamic data and 6-minute walk for analysis at the last meeting. The committee requested more information on the nature and treatment of the infusion site pain.

With respect to the Steering Committee, there were apparently two steering committees. One committee for North American sites and the members were Drs. Barst, Rich, Rubin, Crow and Blackburn. A second committee labeled the European Steering committee. The members of this committee were Drs Rubin, Simonneau, Galie, Naeiije, Crow and Blackburn. Drs Rubin, Crow and Blackburn were inviolved with both committees. Meeting dates were as follows: 16 December 1998 (North American), 2 March 1999 (European), 28 April 1999 (North American), and 7 November 1999 (both North American and European)

The only changes to the submitted protocols were made at the 16 December 1998 meeting. This meeting occurred approximately 1 month after the first subject was enrolled into study P01:04 and several days after the first subject enrolled into study P01:05. The changes were in response to a FDA teleconference call. The changes can be summarized as follows. 1) A global QOL in the form of the Minnesota QOL questionnaire was added to the assessments at weeks 1, 6, and 12. 2) The interim

[79] *Subject 04503 developed sepsis secondary to an elective abortion and died while on study drug. The database captured this patient as a discontinuation due to AE. This error was discovered after the data base lock.*

efficacy assessment was dropped. 3) The last value carried forth approach was used. 4) The Ultrafast CT was incorporated to rule out thromboembolic disease. These changes were incorporated in the protocol by Amendment #3.

A.4.4.4 Conduct

There were 60 subjects whose were stratified inaccurately. Thirty-one of these subjects were vehicle treated subjects and 29 were UT-15 treated subjects. The specifics are shown in Table 47 below:

Table 47. Mistakes in stratification (P01:04-05)

	Vehicle	UT-15
Stratified as primary disease—really secondary pulmonary hypertension	1	1
Stratified as secondary disease—really primary pulmonary hypertension	2	4
Stratified as low exercise—really high exercise	2	6
Stratified as high exercise—really low exercise	8	4
Stratified as high exercise but exercise exceeds upper limits allowed	0	2
Mis-stratified as low exercise capacity and secondary pulmonary hypertension and vasodilator use—in reality high exercise capacity, primary disease and no vasodilator use	1	0
Stratified as low exercise capacity and no vasodilator use—really high exercise capacity and yes vasodilator use	1	1
Stratified as high exercise capacity and vasodilator use—really low exercise capacity and no vasodilator use	1	1
Stratified as primary pulmonary disease with vasodilator use—really secondary pulmonary hypertension with no vasodilator use	3	3
Stratified as vasodilator use—really no vasodilator use	4	4
Stratified as no vasodilator use—really vasodilator use	8	3

There was no overwhelming bias in the errors in of stratification. The mITT considers subjects with appropriate stratification. The pITT analysis considers these subjects as randomized.

Blinding. By protocol, the treatment was blinded to both the physician and subject. An additional barrier to unblinding was included. The physician who performed the exercise distance test was not the physician who was in charge of the subject's care. Other metrics, particularly the dyspnea-fatigue index, however, were performed (and often completed) by the treating physician.

Blinding, however, was not perfect. At the end of the 12-week period the blind of each subject was broken to facilitate treatment into long term therapy. Common drug-related adverse events would rapidly be associated with a given treatment, certainly after the subject's treatment was unblinded.

A second and related compromise to the blind of this study is that subjects who were treated with active drug were more likely to have infusion site pain/infusion site reaction. Furthermore, the intensity and severity of such pain, much more frequently required concomitant medications including narcotics and anti-inflammatory drugs among UT-15 subjects than those treated with vehicle. The onset of such pain was early during the course of treatment. It is, therefore, unclear to what extent measurements performed by the treating physician was compromised by the potential unblinding.

Major assessments of those enrolled may have been by an investigator who had a good idea as to the randomized therapy. Most notably, assessments of signs and symptoms of CHF, quality of life measurements, as well as certain important classifications such as the reason for discontinuations were perhaps biased by the knowledge of treatment.

Protocol violations. The sponsor cites the following criteria as major deviations. There were relatively few subjects who deviated from protocol.

Table 48. Protocol deviations (P01:04-05)[80]

	P01:04		P01:05		Pooled	
	Veh	UT-15	Veh	UT-15	Veh	UT-15
Subjects who received the incorrect treatment for any part of the treatment period	1	0	2	0	3	0
Crossed over to alternative study drug during the treatment period	1	0	2	0	3[81]	0
Were in violation of inclusion criteria for diagnosis of pulmonary hypertension the appropriate hemodynamic parameters	2	1	0	2	2	3
Were in violation of exclusion of criteria for portal hypertension, history of left sided disease, other diseases (i.e. sickle cell anemia, schistosomiasis), musculoskeletal disorder that could alter ambulation, or exercise distance between 40-450 m.	0	0	1	0	1	0
Received any prostaglandin (or analogs) therapy for 7 days of the week 12-exercise test	0	0	0	0	0	0
Received chronic concomitant use of iv or inhaled medications to treat PAH	4	4	0	3	4	7
Other protocol violatons considered on an individual basis prior to unblinding (received rescue therapy[82], interstitial lung disease[83].	1	1	1	0	2	1

A.4.4.5 Definitions of subject cohorts used in analyses[84]

The "Pure Intent-to Treat" (or pITT") Is defined as all subjects randomized in either study. Subjects are counted to the group to which they were randomized, regardless of the treatment they were actually given, or whether any study drug was given at all. All original stratification information used in the randomization procedure is used, regardless of whether it was later found to be incorrect.

The "Modified Intent-to Treat" or ("mITT") population is the same as the "pITT" population except that subjects who did not receive either study drug medication were excluded from the analysis. In addition, the efficacy data for any subject who was inadvertently given the alternative treatment during the trial (i.e. crossed over) due to errors in resupply of study medication was censored at the time of cross-over (by not having data after cross-over included in the analysis). Incorrect stratification data was corrected for this cohort.

The "Per-Protocol" population was defined as all subjects in either study who actually receiving study drug for at least 8 weeks and who had baseline and week 12 exercise test assessments or discontinued due to death, transplantation or clinical deterioration. This population excluded subject with major protocol violations, and those who were not receiving study drug during their Week 12-exercise test due to premature discontinuation. Subjects were counted as being in the group corresponding to the treatment they actually received at the start of the dosing period. Subjects who crossed-

[80] *Sponsor's analysis.*

[81] *These are the same subjects who received the wrong treatment.*

[82] *Two subjects on vehicle.*

[83] *One subject on UT-15.*

[84] *Volume 33A, page 6365.*

over to the alternative treatment during the trial were excluded from this cohort. Subjects with the following protocol violations were excluded from this cohort:

- Subjects who violate inclusion criteria #3 and #6.That is, subjects who do not satisfy the criteria for the diagnosis of pulmonary hypertension and exclude left sided cardiac dysfunction.
- Subjects who violate exclusion criteria #9, #10, #11 and #12. That is those with portal hypertension, a history of left sided disease, a history of other diseases (i.e. sickle cell anemia, schistosomiasis), Musculoskeletal disorder that could alter ambulation or who had an exercise distance outside the range of 40-450 meters at baseline.
- Subjects who are treated with prostaglandin or their analogues for pulmonary hypertension.
- Subjects who are treated with chronic or inhaled medications to treat pulmonary hypertension.
- Other protocol violations

The "Safety Population" is defined as all subjects in either study who actually receiving study drug, and all subjects will be counted as being in the group corresponding to the treatment that they actually received. If a subject received UT-15 at any point during the study, they will be counted in that treatment group.

Comment. Subjects who are inadvertently treated with UT-15 should also be included in the denominator of the vehicle group. These subjects were only included in the UT-15 group. The denominator of the vehicle group and consequently, the rate of adverse events was mildly inflated in the vehicle group.

The specifics of the cohorts are shown in Table 49.

Table 49. Cohorts analyzed (P01:04-05)

	mITT	pITT	Per-Protocol	Safety
Randomized manually to correct treatment	Included	Included	Included	Included
Randomized manually, received incorrect treatment weeks 7-12	Included: Efficacy censored at week 6	Included	Excluded	Included
Incorrect stratification information	Included: Stratification information corrected	Included: Stratification information not corrected	Included: Stratification information corrected	Included: Stratification information corrected
Only one assignment available at site	Included	Included	Included	Included
Received drugs for < 8 weeks	Included	Included	Excluded	Included
Subjects who did not have the diagnosis of pulmonary hypertension or did not have the requisite hemodynamics	Included	Included	Excluded	Included
Subjects who had Portal hypertension, left sided failure, other diseases that cause pulmonary hypertension, musculoskeletal disorders or 6-minute walk outside 50-450 m	Included	Included	Excluded	Included
Subjects with premature discontinuations aside of death, deterioration or transplant	Included	Included	Excluded	Included

The distribution of subjects by stratification cohort is shown in Table 50.

Table 50. Subjects by stratification cohort (P01:04-05)

Stratum[85]			pITT			mITT		
PH	**Exer**	**Vaso**	**Veh**	**UT-15**	**Total**	**Veh**	**UT-15**	**Total**
1°	High	—	133	129	262	132	130	262
	High	—	7	5	12	4	4	8
2°	High	Yes	37	39	76	44	40	84
		No	54	53	107	51	56	107
	Low	Yes	2	2	4	3	0	3
		No	4	5	9	2	3	5

There were few subjects with low exercise performance. Slighly more than half the subjects were stratified as primary pulmonary hypertension with high exercise performance.

Concomitant symptoms at baseline are shown in Table 51. The most common symptoms at baseline were dyspnea on exertion, exercise intolerance and fatigue. The remaining symptoms are listed in approximate decreasing frequency.

[85] *Primary or secondary pulmonary hypertension; high or low exercise capacity; receiving or not receiving vasodilators.*

Table 51. Symptoms at baseline (P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Dyspnea on exertion	109 (98)	110 (97)	125 (100)	120 (100)	234 (99)	230 (99)
Exercise intolerance	97 (87)	109 (97)	110 (88)	115 (96)	217 (92)	224 (96)
Fatigue	97 (87)	106 (94)	107 (86)	105 (88)	204 (86)	211 (91)
Palpitation	50 (45)	60 (53)	50(40)	61 (51)	100 (42)	121 (52)
Dizziness	54 (49)	58 (51)	53 (42)	61 (51)	107 (45)	119 (51)
Peripheral edema	53 (48)	52 (46)	58 (46)	44 (37)	111 (47)	96 (42)
Edema	53 (48)	52 (46)	58 (46)	44 (37)	111 (47)	96 (41)
Chest Pain	43 (39)	46 (41)	48 (38)	49 (41)	91 (39)	95 (41)
Weakness	34 (31)	41 (36)	37 (30)	48 (40)	71 (30)	89 (38)
Orthopnea	35 (32)	44 (39)	38 (30)	32 (27)	73 (31)	76 (33)
Cyanosis	27 (24)	30 (27)	56 (45)	45 (38)	83 (35)	75 (32)
Hypoxia	26 (23)	25 (22)	56 (45)	48 (40)	82 (35)	73 (31)
Cough	35 (32)	38 (34)	34 (27)	30 (25)	69 (29)	68 (29)
Cool extremities	38 (34)	38 (34)	44 (35)	29 (24)	82 (35)	67 (29)
Lightheadedness	28 (25)	34 (30)	31 (25)	33 (28)	59 (25)	67 (29)
Right heart failure	32 (29)	31 (27)	39 (31)	26 (22)	71 (30)	57 (25)
Headache	17 (15)	26 (23)	16 (13)	22 (18)	33 (14)	48 (21)
Low cardiac output	15 (14)	19 (17)	23 (18)	23 (19)	38 (16)	42 (18)
Musculoskeletal pain	17 (15)	25 (22)	20 (16)	15 (13)	37 (16)	40 (17)
Tachycardia	14 (13)	22 (20)	19 (15)	16 (13)	33 (14)	38 (16)
Arrhythmia	11 (10)	17 (15)	18 (14)	16 (13)	29 (12)	33 (14)
Angina	7 (6)	13 (12)	15 (12)	19 (16)	22 (9)	32 (14)
Depression	20 (18)	19 (14)	18 (14)	15 (13)	38 (16)	31 (13)
Paroxysmal nocturnal dyspnea	7 (6)	14 (12)	10 (8)	15 (13)	17 (7)	29 (12)
Dyspnea at rest	8 (7)	17 (15)	19 (15.	9 (8)	27 (11)	26 (11)
Nausea	9 (8)	16 (14)	13 (10)	9 (8)	22 (9)	25 (11)

Baseline medications. Baseline classes of medications are shown in Table 52. The vast majority of subjects were on some class of medications at baseline. The proportion of subjects in both groups on each class of medication was similar. Approximately 2/3 of those enrolled was anti-coagulated at baseline. Loop diuretics were used in approximately 45% of those enrolled. Steroids were actually infrequently used (< 10% of those enrolled] despite the 90 subjects whose etiology of pulmonary hypertension was due to collagen vascular disease.

Table 52. Baseline medications (P01:04-05)

	Veh N=236	UT-15 N=233		Veh N=236	UT-15 N=233
Any	226 (96)	219 (94)	ACE-inhibitors/Angiotensin blockers	29	23
Loop diuretics	103	105			
Oxygen	85	83	Steroids	18	16
Calcium channel blockers	100	98	Anticoagulants/anti-platelets	166	153
Digitalis compounds	56	57	Diuretics (incl spironolactone)	62	73

A.4.4.6 Dosing

The dose level of UT-15 (or vehicle) was predicated on increasing the dose of drug to a point where signs and symptoms of pulmonary hypertension are improved, balanced against any dose-related adverse event profile of the drugs. The dose of drug (or vehicle)

was increased if the signs and symptoms of pulmonary hypertension were not improved or if the subject's clinical condition deteriorated.

The dose of drug (vehicle) was not to be increased or was to be decreased if there were any of the following:

- Changes in hemodynamics, vital signs, or clinical signs or symptoms (e.g. lightheadedness).
- Onset of an adverse experience associated with study drug (headache, nausea, emesis. restlessness and anxiety, or
- Pain at the infusion site (either new onset or worsening of pain).

The mean infusion rates for both vehicle and UT-15 are shown in Figure 11. At the end of the period the infusion rate of UT-15 (mean ±SD) was 9.3 ± 5.4 µg/kg/min and that for vehicle was 19.1 ± 4.8 µg/kg/min. The lower doses of U-15 reflects the limitation imposed by the onset of adverse events or excessive pharmacological effect or UT-15 and should not be construed as demonstrating a benefit of UT-15 in ameliorating the signs and symptoms of pulmonary hypertension.

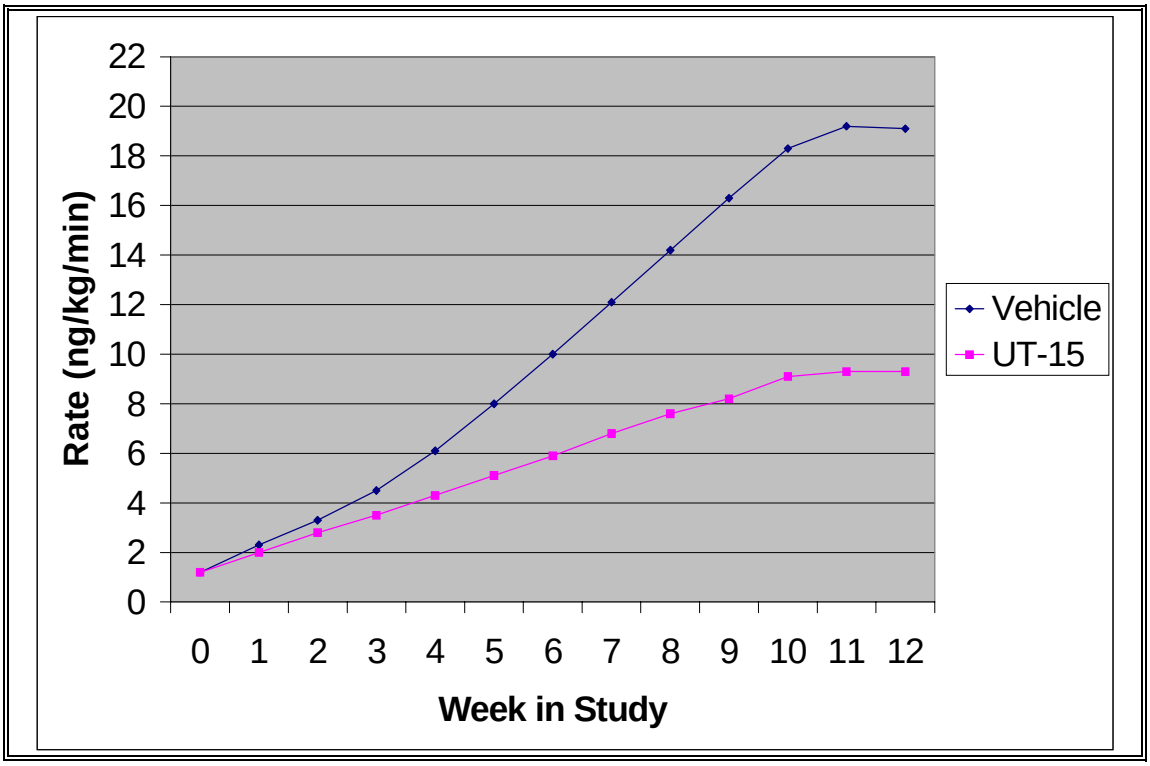


Figure 11. Mean infusion rate by week in study (P01:04-05)

More vehicle subjects were titrated upward than UT-15 subjects (Figure 12). The greater number of such subjects could either reflect the greater need for increased dosing (i.e. a measure of increased benefit for UT-15) or conversely the marginal tolerance of the UT-15 dose so that further dose increases were not well tolerated. More UT-15 subjects required dose reductions than vehicle subjects. Sponsor's Listing 16.2.5.3 only lists the reason for dose changes. The usual reasons for downward change was due to pain at the infusion sites. No reason was listed for not increasing the dose.

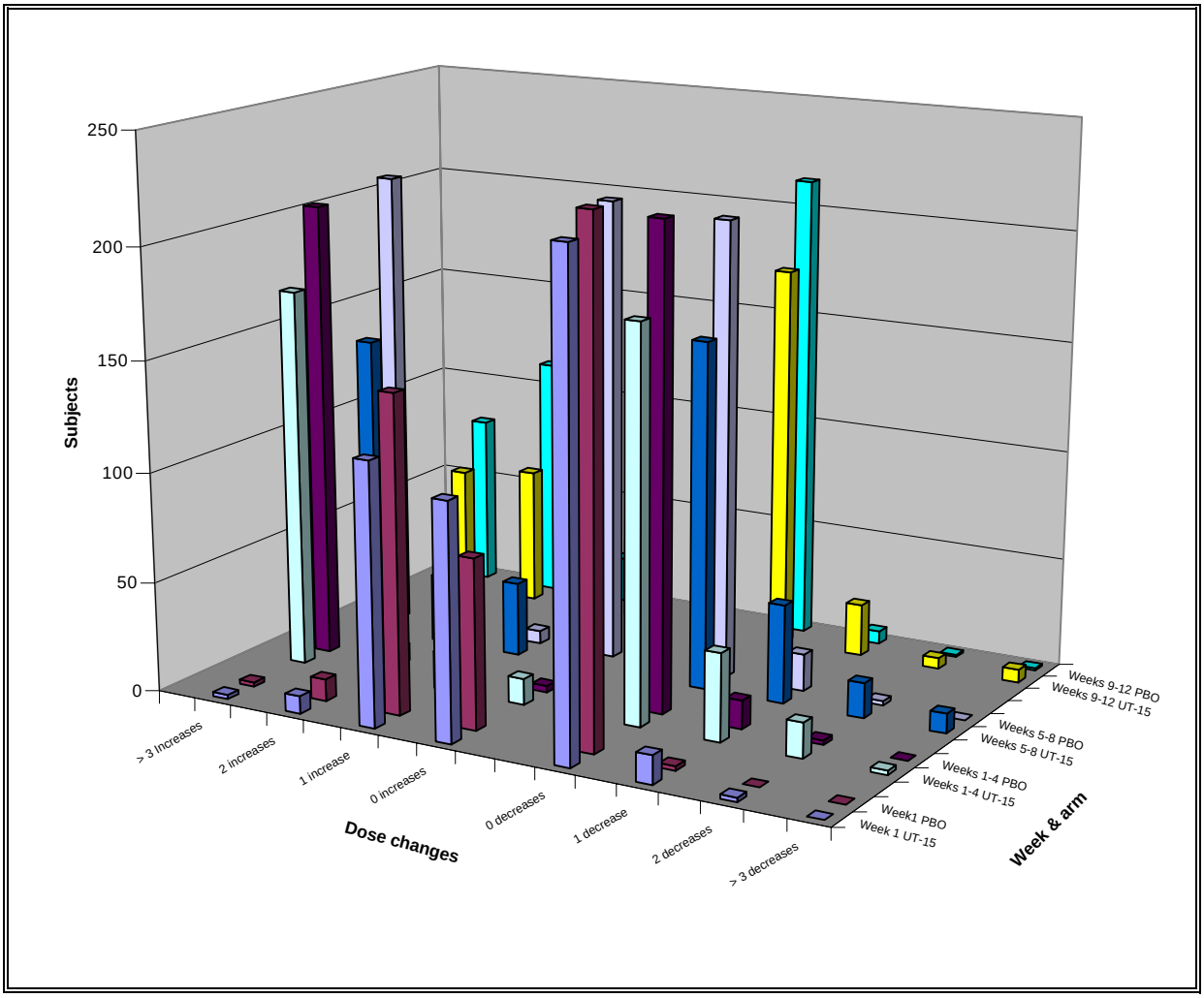


Figure 12. Changes in dose by time in study (P01:04-05)

Adverse events limiting dose. Infusion with UT-15 was less well tolerated than vehicle. Based on the data in Listing 16.2.5.3, ninety-five UT-15 subjects had dose reductions at least once for either infusion site pain or infusion site reaction. An additional twenty-nine had the dose reduced due to excessive pharmacologic function. For those treated with vehicle there was one subject who had the dose decreased due to adverse events related to infusion site pain or reaction and three for excessive pharmacologic effect.

The sponsor also supplies concomitant medications that were required to mitigate pain (redness, bruising, burning or pain). Of the subjects treated with UT-15, 207/ 233 (89%) with data available required some medications for infusion site reaction (pain or erythema). Only 35 /237 vehicle subjects (15%) required medication for infusion site reactions. The medications, which were used to treat these symptoms, ranged from narcotics, anti-inflammatory oral agents to topical steroids, astringents and irritants. More UT-15 required opiate antagonists than vehicle subjects (68 versus 3). There were more subjects treated with UT-15 who required some form of anti-inflammatory medication than those treated with vehicle (131 versus 8).

There were more subjects who discontinued from active treatment than from vehicle. Of the 233 subjects who were randomized to active UT-15, 33 discontinued prior to the

week-12 end point (see Figure 1.2). Eighteen of these subjects discontinued due to adverse events. Seventeen of these subjects had some degree of pain as the attributed reason for discontinuation. Among the 237 subjects who received vehicle, there were 15 subjects who did not complete the 12-week study period. None of these subjects discontinued for site pain.

In summary, UT-15 infusion causes complications at the infusion site at a much greater frequency and greater intensity than vehicle infusion and consequently, these subjects required more frequent and more intense treatment for this pain. This asymmetry of infusion pain across treatments has some consequences. It is quite likely that the investigator had a good idea which subject was receiving active drug and which was receiving vehicle.

Since a blinded, designated, investigator supervised the pivotal six-minute walk, this reviewer does not believe this measurement was compromised. The more frequent pain in the UT-15 infusion group, however, may have compromised the analysis of this metric in a subtler way. Since subjects who discontinued for worsening heart failure are assigned the worst outcomes, whereas those who discontinued for adverse event are given their last observation carried forward, the attribution of a cause of discontinuation is intimately alters the imputed value that was used in the pivotal analysis.

The implications of the much more frequent infusion pain can be considered by the following example. Consider two subjects, one treated with UT-15 and one treated with vehicle that had exactly the same disease course. Both subjects had early and persistent deterioration. The subject treated with UT-15 has some infusion site pain, perhaps even severe in nature. Neither subject was feeling particularly better with respect to their underlying pulmonary hypertension. In fact, these subjects may have been feeling worse. Only the UT-15 subject had the concomitant infusion-site pain and discontinued early. Both subjects eventually went on to die, receive transplant or deteriorate by the criteria of the study. However, only the vehicle subject was treated as the worst outcome. The UT-15 subject who died, deteriorated or was transplanted early was censored and the last observation carried forward. The last observation may have been distant to the time of discontinuation and might not have captured the entirety or even a substantial portion of the status of the subject at the time of the event. Although the study planned to perform exercise measurements on all subjects at 12-weeks, even among those who discontinued, in general, this measurement was not performed. Subjects did not have their status at the end of the study i.e. for 84 days with a window of 71-100 days, with regards to deterioration, death or transplantation ascertained.

If one accepts the possibility that those who ostensibly discontinued for infusion site pain also potentially had a component of worsening disease, then the six minute walk that uses a last observation carried forward analysis produces a more optimistic outcome particularly for the treatment group. The consequence of this asymmetry in adverse events is explored in conjunction with the reviewer's analysis (see section xxxx).

A.4.4.7 Efficacy

A.4.4.7.1 Walking distance

Baseline measurements. The baseline walk-distance (per sponsor) for study 01:04 and 01:05 are shown in Table 53. The distances are relatively consistent across studies. It should be appreciated that a reasonable walking distance for a healthy individual, assuming a 20-minute mile would be approximately 480 meters. Subjects with high baseline measurements, therefore, had modest upside potential. The analysis treated baseline-walking distance as a monotonic covariate and consequently did not correct for differences in exercise performance at the extremes of baseline measurements.

Table 53. Baseline walking distance (P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=233
Mean±SE	336±8	327±8	319±8	326±8	327±6	326±5
Median 25-75 percentile	349 272-377	341 264-390	338 272-377	349 270-396	342 272-397	345 264-395
P-value	0.32		0.50		0.85	

Effect of UT-15 on six-minute walk. The sponsor performed a multitude of analyses of the six-minute walk data. There is a general consistency across all analyses. Neither of the two studies by themselves was statistically significant by most of these analyses. The p-value for the pooled studies as performed by the sponsor was, in general, less than $p<0.01$, but never so overwhelming as to be <0.00125. As such, even by the sponsor's own rules or by the criteria usually proposed by this Division this study could not be considered as sufficient for drug approval.

There were, moreover, ambiguities in the statistical plan as proposed by the sponsor, Dr. Lawrence, the FDA statistician reanalyzed the data by treating the data consistent with the protocol but different to that as performed by the sponsor.

This reviewer performed an alternate set of analyses. The starting point of these analyses revolved around the asymmetry of the study design. The default algorithm for assigning a walk distance for subjects who discontinue without a 12-week walk is shown in Table 1.19. Those subjects who discontinued due to adverse events had their last observation imputed. Those who discontinued either due to death, transplantation or deterioration were treated as a worse outcome. For the non-parametric analysis those who discontinued due to death, deterioration or transplantation were assigned a worst rank, in the non-parametric analysis they were assigned a walking distance of zero feet.

There are several consequences to the imbalance in discontinuations. First, those who discontinue due to adverse events could never receive a worst outcome whereas those who were in the vehicle group could potentially receive the worst outcome due to death, transplantation or deterioration. Second, it is unclear to what extent the attribution of a discontinuation would be preferentially assigned to infusion related problems as opposed to deterioration of status. Third, the imputed value could be so distant to the time of discontinuation that it inaccurately reflects the status at the time of discontinuation. The imputed value would be clearly inaccurate. Lastly, the asymmetric use of medications that may alter hemodynamics could also bias any interpretation of the results.

Since there were many more subjects in the UT-15 group who were discontinued due to ADRs, these subjects could never receive the worst outcome. The analyses performed by this reviewer attempt, in a step-wise manner, to test the consequence of the asymmetry in discontinuations.

The first analysis performed by this reviewer consists of imputing a worse value to those who died, were transplanted during the window of the study (till day 100). These outcomes are not subjective and corrections could easily be performed. The second analysis treated those deaths, transplantation as worst outcomes but also added those who were started on flolan within a month of discontinuing UT-15 and within the 100-day window of the study as worst outcomes. This analysis was based on the assumption was that those who were relatively rapidly started on flolan had some deterioration in status that transformed the optional need for flolan at baseline to the treatment of choice. A third analysis also treated as worst outcomes all those who were

started on flolan during the 100-day window of the study whether they were started within a month or after a month of stopping. Lastly, there was an occasional subject whose status was clearly worse than the LOCF value would imply. In general, the LOCF was at a time point distant to when the subject discontinued. It seemed counter-intuitive to impute a very favorable value where the course was clearly downhill. These subjects were censored without the positive walking distance imputed.

By either Dr. Lawrence's or this reviewer's analyses, the p-value for the pooled studies exceeds p>0.01.

Table 54. Imputation rules for subjects without a week 12 walk (P01:04-05)

	Alternative 1		Alternative 2	
	Non-parametric	**Parametric**	**Non-parametric**	**Parametric**
Death within 12-weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Clinical decompensation within 12 weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Transplantation	Last standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Accidents or death unrelated to disease or study	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
AE (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Lost to Follow-up (survivor, Week 12	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Consent withdrawn (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*

Sponsor's analysis #1

Database: Pooled studies P01:04 and P01:05.

Type of Analysis: Non-parametric analysis of covariance (covariates included: baseline distance walked, center, etiology of pulmonary hypertension (primary versus secondary) and vasodilator use at baseline. Later added a covariate was use of steroids to treat primary pulmonary hypertension).

Population: mITT.

Subjects excluded: One subject with no post baseline measurement (UT-15, pt# 10507), one subject who withdrew before receiving any dose (vehicle; pt # 07501) and three UT-15 subjects were excluded (#05010; #08008 and #66006) because of the absence of other subjects in their stratification cells for baseline walk. The primary analysis, however was modified to remove baseline walk as a stratification variable, to allow inclusion of these three subjects. Baseline walk was used as a continuous covariate, allowing these three subjects to be included.

Imputation methods: Lowest rank assigned to deaths, transplants or clinical deterioration (defined as rescue with either chronic i.e. longer than five days with intravenous medication, chronic inhaled medications other than oxygen or chronic use of prostaglandin analogues). For other missing values the last standard rank in the exercise hierarchy was carried forth.

The results of this analysis are shown in ble 55.

Table 55. Change in 6-min walk (sponsor's analysis #1[86]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Median	1	3	-3	16	0	10
25th,75th percentile	-53, 31	-27, 37	-38, 35	-22, 50	-45, 33	-28, 48
P-value	0.06		0.06		0.006	

The median overall magnitude of effect for the pooled studies was quite small (10 meters or approximately 3% of baseline walk distance) for the pooled studies. None of the individual studies was statistically significant by the standard criteria.

Sponsor's analysis #2

Database: Pooled studies P01:04 and P01:05.

Type of analysis: Non-parametric analysis of covariance [covariates included: baseline distance walked, center, etiology (primary versus secondary) and vasodilator use at baseline]. Later added as a covariate was use of steroids to treat primary pulmonary hypertension)

Population: pITT (see Table for definition of this cohort). The population differs from the mITT in several respects. The key differences are that those subjects who were inadvertently crossed over were included in their randomized group and not the cross-over group. In addition, those who were incorrectly stratified were left analyzed in the incorrect stratification.

Imputation methods: Lowest rank assigned to deaths, transplants or clinical deterioration. For other missing values the last standard rank in the exercise hierarchy was carried forth.

The results are shown in Table 56.

Table 56. Change in 6-min walk (sponsor's analysis #2[87]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=126	UT-15 N=120	Veh N=237	UT-15 N=233
Median	1	3	-2	16	0	10
25th,75th percentile	-53, 31	-27, 37	-37, 35	-20, 50	-43, 32	-24, 47
P-value	0.06		0.06		0.009	

Sponsor's analysis #3

Database: Pooled data studies P01:04 and P01:05.

Population: mITT.

Type of analysis: Parametric analysis. (ANCOA) with the covariates [baseline walk distance, center, etiology of pulmonary hypertension (PPH versus other), vasodilator use at baseline (yes versus no)].

---

[86] *mITT population, lowest rank imputed for deaths, dropouts and discontinuations and LOCF for those who discontinue due to adverse events, non-parametric analysis of covariance.*

[87] *pITT analysis Lowest rank imputed for deaths, dropouts and discontinuations and OCF for those who discontinue due to adverse events, non-parametric analysis of covariance. P-values are nominal.*

Imputation method: Subjects who died, received transplant or clinically deteriorated a value of zero meters was imputed for the final analysis. Subjects who discontinued for adverse events were given the last value carried forth.

Table 57. Change in 6-min walk (sponsor's analysis #3[88]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Baseline mean	336±8	327±8	319±8	327±8	327±6	327±5
Change	-29±10	-2±9	-15±8	-2±10	-22±6	-2±7
P-value	0.04		0.4		0.04	

Note: This analysis shows only one study with statistical significance and this study drives the pooled analysis. The overall pooled analysis does not approach the pre-specified 0.01.

Sponsor's analysis #4

Database: Pooled data P01:04 and P01:05

Population: mITT cohort

Type of analysis: Non-parametric analysis

Imputation method: For this analysis, six minute walk distances were censored at the time of study discontinuation for any reason and the last standardized rank before discontinuation was carried forth even for those who discontinued due to death deterioration or for missing data.

Table 58. Change in 6-min walk (sponsor's analysis #4[89]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Median	4	7	3	16	3	11
25th,75th percentile	-39, 37	-23, 37	-33, 36	-17, 50	-35, 34	-21, 48
P-value	0.08		0.07		0.01	

The FDA statistical reviewer's analyses

The analyses performed by the sponsor treated some subjects whose treatment in the primary analysis was somewhat ambiguous. The discussion below is culled from the statistician's review.

[88] *mITT population, Lowest rank imputed for deaths, dropouts and discontinuations and OCF for those who discontinue due to adverse events, parametric analysis of covariance. P-Value is nominal*

[89] *Non-parametric analysis of covariance, All patients who discontinue due to any reason will have the LOCF imputed.*

Table 59. FDA statistician's handling of missing data.

Study/ Subject Treatment	Issue	Statistician's comment
04/7004 UT-15	This subject had a valid baseline week 1 and week 12 data. Week 6 data missing because subject too sick to exercise	The statistician cites the wording in the analysis plan … "If an exercise test is missing because subject was too critically ill" the lowest standardized rank will be used for the nonparametric analysis and a distance of " 0 meters" will be used for the parametric analysis. Data missing for other reason will have the last standardized ranks carried forward for the nonparametric analyses and last observation carried forward for the parametric analyses". The statistician analyzed such subjects as a worst outcome.
05/61008 Vehicle	This subject had a valid baseline week 1 and week 12 data. Week 6 data was missing because the subject was too sick to exercise.	
04/10507 UT-15	This subject had a baseline walking distance but no subsequent measurements since the subject dropped out on day 9 for an adverse event. The sponsor censors this subject.	The FDA statistician proposed two additional ways of handling the data. Fit a regression to baseline versus he remaining covariates and carry forward the standardize rank for this subject Carry forward the worst rank Subjects who do not have complete follow up are imputed by carrying forward the last value after adjusting for several covariates. Using this approach will tend to carry forward a smaller rank (worse outcome). For this subject the standardized rank carried forward was 0.138
05/52006 Vehicle	This subject had baseline and one post-baseline measurement. This subject was discontinued for an ADR. The subject died within 100 days of randomization.	A worst outcome was imputed for this subject
05/60005 Vehicle	This subject dropped informed consent after 46 days, however, a 12-week walking distance was performed.	The sponsor used the rank of the 12 week assessment. The statistician used the 6 week rank
04/2004 05/52003 05/52004	These subjects all received Vehicle for 6 weeks but were inadvertently switched to UT-15 after 6 weeks. The sponsor Carried Forward the standardized risk from week 6	The FDA statistician's analysis uses the 12-week measurement
05/18501 Vehicle	This subject had three measurements of on-treatment a 35, 55 and 71 days, The first two of these measurements would satisfy the criteria for the 6-week visit. The last did not fall within the window for the 12-week visit. The sponsor treated the day 71 visit as the week 12 visit.	The FDA statistician found the rank on Day 55 and carried the rank for this measurement forward.

Lastly the FDA statistician proposes to handle the few subjects stratified to low baseline walk distance (< 150 M) different than the sponsor. The sponsor, because of the few subjects with low baseline measurements analyzed the data without baseline measurements as a covariate. The FDA statistician used baseline distance as a covariate and finds the significance of the means core statistic from the permutation distribution.

Table 60. Nominal p-values from FDA statistician's analyses (P01:04-05)

	P01:04	P01:05	Total
P-value	0.10	0.08	0.015

FDA Medical Officer additional analyses

There was clearly an asymmetry in discontinuations in the study. Those who were treated with active drug were far more likely to discontinue due to infusion site pain. In fact, infusion site pain was nearly pervasive among those who were infused with active drug but infrequent among those infused with vehicle. Subjects who discontinued for adverse events were censored at the time they were discontinued. The consequence of this algorithm was that these subjects could never be saddled with the worst possible outcome for death, deterioration or transplant. This algorithm biases the analysis, favoring UT-15. The number of subjects that discontinue because of pain may have had some component of worsening of status provoking their discontinuation. Lastly, those who had values imputed may have been within the window of the next measurement but did not have this measurement. The imputed value may not reflect the status at the time of discontinuation.

Table 61 contains summaries of those who discontinued prematurely. The information was collected from the sponsor's narratives for those who discontinued (pp5680-522) as well as data contained within a supplement (dated 11 January 2001.

Dr, Lawrence, the FDA statistician, performed the three analyses that were requested by this reviewer. The first analysis included only those subjects who were discontinued as ADR but died or required transplantation (non-subjective outcomes) and treated those as worse outcomes. The second analysis also treated as worse outcomes, subjects who were discontinued because of adverse reactions but were started on Flolan within one month of discontinuation and within the 100-day upper limit of the window of the 12-week visit. The third analysis further incorporates all subjects who were started on Flolan within the 100-day window of the study whether they were started within 1-minth of discontinuation or not. In addition, there were one or two subjects whose values as a LOCF seem so inconsistent with their status as described by the sponsor and a later walk-test could or should have been performed. These subjects were excluded without the LOCF. There were additional subjects whose histories could be interpreted to represent worsening status, however, these subjects did not fall into any of the described categories. These subjects were treated as per sponsor's analyses.

The sponsor submitted narratives for those who discontinued (P 5680 –5722). The sponsor also submitted supplement (dated 11 January 2001) that was used to complete Table 61. The sponsor's analysis of these events differ from that of the reviewer (this reviewer has taken a very conservative approach).

The sponsor's did not consider any of those who discontinued as adverse events as having decompensated. There analysis is appended.

Table 61. Reviewer's handling of discontinuations for ADR or WC (P01:04-05)

Study Subject Class[90] Arm	Description	Classification by reviewer
01:04/ 2001 ADR UT-15	This was a 42-year old female with NYHA Class III heart failure associated with pulmonary hypertension as a consequence of congenital heart disease who was titrated to a maximum infusion rate of 5.0 ng/kg/min. The subject was discontinued from treatment after 43 days due to intolerable infusion site pain, nausea and vomiting. Dyspnea on exertion worsened 2 days after discontinuation. Approximately 6 weeks later (within the 100-day window) the subject was initiated on Flolan following a pulmonary hypertensive crisis. Day: 1 | 8/9 | 43 Six minute walk in meters: 479 | 446 | 132 Dyspnea fatigue index score: 6 | 6 | 6	Worse outcome by analysis # 3. The subjects exercise performance deteriorated before the subject discontinued and the subject eventually crashed and required flolan. This subject clearly had deterioration during the time course of the study.
01:04/ 2006 ADR UT-15	This was a 42-year old female with NYHA Class III heart failure associated with pulmonary hypertension as a consequence of SLE. The maximum dose of UT-15 was 2.5 ng/kg/min. The dose was reduced a s a consequence to infusion site pain and discontinued on day 71. Within two weeks the subject was started on flolan. Day: 1 | 8/9 | 43 Six minute walk in meters: 388 | 470 | 495 Dyspnea fatigue index score: 6 | 6 | 6	Worse outcome by analysis # 2 The subject received Flolan within two weeks of discontinuation.. The closest exercise test and dyspnea fatigue index was approximately 1 month prior to discontinuation and may not reflect the status of the subject.
01:04/ 2016 ADR UT-15	This was a 49-year old female subject with a 14-year history of pulmonary hypertension and NYHA Class III associated with congenital heart disease. The maximum dose of UT-1 was 3.75 ng/kg/min. The subject discontinued on day 47. The subject experienced worsening pulmonary hypertension after discontinuation of infusion. The subject was alive 30 days post dose. The subject was started on flolan four-months post discontinuation and therefore after the 100 day window. Day: 1 | 5 Six minute walk in meters: 198 | 406 Dyspnea fatigue index score: 2 | 5	This subject was censored with no LOCF, per analysis #3.. The sponsor suggests the deterioration was a consequence of discontinuing UT-15. This subject's carried forward value was extremely good. The six-week measurement was never performed although the time of discontinuation was within the window for this measurement.
01:04/ 2020 ADR UT-15	This was a 33-year old female subject with a six-month history of primary pulmonary hypertension. The subject received as their maximum dose 1.3 ng/kg/min. After a total of 5-weeks of therapy UT-15 was discontinued because of intolerable site pain. The subject elected to start intravenous flolan within one month. Day: 1 | 9 Six minute walk in meters: 264 | 347 Dyspnea fatigue index score: 8 | 8	Worse outcome by analysis # 2. Although elected to start flolan it is possible to construe as a worse change in status. The sponsor claims the subject's status was improved. It is therefore, unclear why flolan was needed. The subjects discontinuation fell within the six week visit window. It is unclear why no exercise test was performed prior to discontinuation.

[90] *ADR = adverse drug reaction; WC = withdrew consent*

<table>
<tr><th>Study
Subject
Class[90]
Arm</th><th>Description</th><th>Classification by reviewer</th></tr>
<tr><td>01:05/
4503
ADR
UT-15</td><td>This was a 36-year old female with primary pulmonary hypertension and NYHA Class III. The subject received a maximum infusion of 5.0 ng/kg/min. The subject became septic as a consequence of a chemical abortion. The subject was febrile. The subject arrested and died three days later.
<table>
<tr><td>Day</td><td>1</td><td>8</td><td>45</td></tr>
<tr><td>Six minute walk in meters</td><td>375</td><td>340</td><td>362</td></tr>
<tr><td>Dyspnea fatigue index score</td><td>6</td><td>3</td><td>5</td></tr>
</table></td><td><u>Worst outcome by analysis #1.</u>. This subject was treated as a Adverse Event and should be treated as a worse outcome since the subject died during the time window of the study.</td></tr>
<tr><td>01:04/
5009
ADR
UT-15</td><td>This was a 51-year old female Caucasian subject with NYHA Class III associated with a congenital systemic to pulmonary shunt. The maximum dose was 1.25 ng/kg/min. The subject discontinued after approximately 6 weeks due to continuous, moderate infusion site pain. The subject was not titrated upward and remained on the 1.2 ng/kg/min dose. The subject was alive approximately 1 month later. This subject did not receive flolan post discontinuation.
<table>
<tr><td>Day</td><td>0/1</td><td>9</td><td>42/43</td></tr>
<tr><td>Six minute walk in meters</td><td>337</td><td>253</td><td>276</td></tr>
<tr><td>Dyspnea fatigue index score</td><td>7</td><td>3</td><td>3</td></tr>
</table></td><td><u>Worse outcome by analysis #2</u>. The subject had a decrease in exercise performance and a marked worsening of the dyspnea fatigue index.</td></tr>
<tr><td>01:04/
7004
ADR
UT-15</td><td>This was a 44-year old Caucasian female, NYHA Class II as a consequence of systemic shunts The subject discontinued medication on study on day 25 due to infusion site pain. The subject was subsequently hospitalized due to hemoptysis. The maximum dose was 1.0 ng/kg/min. The subject was alive This subject did not receive Flolan.
<table>
<tr><td>Day</td><td>0/1</td><td>10</td><td>44/45</td><td>87</td></tr>
<tr><td>Six minute walk in meters</td><td>345</td><td>393</td><td>Too ill</td><td>398</td></tr>
<tr><td>Dyspnea fatigue index score</td><td>7</td><td>6</td><td>7</td><td>6</td></tr>
</table></td><td><u>This subject had an off-treatment measurement at week 12.</u> This value was used. by the sponsor. This subject did not fit into the categories for worst outcome but was too ill at last visit. This patient could have been treated as a worst outcome but was censored.</td></tr>
<tr><td>01:05/
10507
ADR
UT-15</td><td>This was a 45-year old female NYHA Class IV with her pulmonary hypertension secondary to Eisenmennger's syndrome. The subject was treated only 9 days due to infusion site pain. The subject was alive 30 days later. This subject received an elective transplant two months later.
<table>
<tr><td>Day</td><td>2</td><td>9</td></tr>
<tr><td>Six minute walk in meters</td><td>183</td><td>—</td></tr>
<tr><td>Dyspnea fatigue index score</td><td>1</td><td>3</td></tr>
</table></td><td><u>Worse outcome by analysis #1</u>. This subject was transplanted during the window of the study. The fact that it was elective is not prespecified as mitigating to worse outcome</td></tr>
<tr><td>01:04/
11002
ADR
UT-15</td><td>This was a 49-year old female subject with PPH and NYHA Class II. The subject received a maximum dose of 2.5 ng/kg/min. The subject discontinued on day 31 of treatment. The subject was alive one month after discontinuation. This subject received Flolan 2 months post –discontinuation.
<table>
<tr><td>Day</td><td>1/2</td><td>9</td><td>30</td></tr>
<tr><td>Six minute walk in meters</td><td>370</td><td>381</td><td>229</td></tr>
<tr><td>Dyspnea fatigue index score</td><td>4</td><td>4</td><td>3</td></tr>
</table></td><td><u>Worse outcome by analysis # 3</u>. The subject's exercise capacity deteriorated by day 30. The subject received flolan during the window of the study. The subject's exercise performance was going downhill.</td></tr>
<tr><td>01:04/
11003
ADR
UT-15</td><td>This was a 28-year old female with NYHA Class III and pulmonary hypertension secondary to Eisenmenger's syndrome. The subject was discontinued after 45 days. The subject was alive one month after discontinuation. The subject was started on Flolan 3 months after discontinuation, outside the window of the study. No statement re inotropic support was made. This subject did not have a six-minute walk performed at week 6.</td><td><u>Censored</u> a LOCF analysis is appropriate. This subject was censored on day 45. I have concern as to why the subject did not have a six-minute walk test at week 6. The start of Flolan was outside the study window.</td></tr>
</table>

Study Subject Class[90] Arm	Description	Classification by reviewer
	<table><tr><td>Day</td><td>-11</td><td>1</td><td>7</td><td>36</td></tr><tr><td>Six minute walk in meters</td><td>287</td><td>—</td><td>323</td><td>—</td></tr><tr><td>Dyspnea fatigue index score</td><td>—</td><td>2</td><td>2</td><td>2</td></tr></table>	
01:04/ 14012 ADR UT-15	This was a 61-year-old female subject with NYHA class III with pulmonary hypertension as a consequence of systemic sclerosis. The subject received a maximum dose of 6.25 ng/kg/min. The subject was discontinued on day 58 due to severe infusion site pain. The subject developed shortness of breath after discontinuation. The subject was alive 1-month and apparently did not receive flolan. Six minute walk in meters (day): <table><tr><td>Day</td><td>1/2</td><td>9</td><td>44</td><td>58</td></tr><tr><td>Six minute walk in meters</td><td>339</td><td>345</td><td>333</td><td>—</td></tr><tr><td>Dyspnea fatigue index score</td><td>6</td><td>6</td><td>6</td><td>9</td></tr></table>	This subject could be considered a worse outcome because of the description of worsened shortness of breath and no statement as to the need for inotropic or flolan. The subject did not fit into the three analytic categories. He was treated as LOCF.
01:04/ 16006 Complete Vehicle	This was a 57-year old female with primary pulmonary hypertension and NYHA Class III The subject developed worsening status but was catheterized, with modest change in hemodynamics (PAPm increased to 104 from 96 mm Hg). O_2 saturation decreased to 43.5%. The subject was to be treated with Flolan but arrested and died prior to the start of Flolan. <table><tr><td>Day</td><td>1</td><td>7</td><td>42/43</td><td>81</td></tr><tr><td>Six minute walk in meters</td><td>329</td><td>312</td><td>264</td><td>—</td></tr><tr><td>Dyspnea fatigue index score</td><td>4</td><td>4</td><td>4</td><td>—</td></tr></table>	Worse outcome by analysis #1. This subject had a 0 meters 6-minute walk as the final measurement, it would make no difference if a worse outcome was imputed.
01:04/ 19001 ADR UT-15	This was 54-year old female with PPH and NYHA Class III. This subject was discontinued from the UT-15 infusion due to infusion site pain on day 7. She subsequently restarted UT-15 after an approximately 2-week hiatus. After an additional two weeks she discontinued again due to infusion site pain. Approximately 2 months later she stared Flolan. Six minute walk in meters (day): <table><tr><td>Day</td><td>1</td><td>8</td><td>41</td></tr><tr><td>Six minute walk in meters</td><td>383</td><td>383</td><td>—</td></tr><tr><td>Dyspnea fatigue index score</td><td>6</td><td>6</td><td>2</td></tr></table>	This subject could be considered a worse outcome but did not fit into the three analytic categories. He was treated as LOCF. The dyspnea fatigue index at the last time point had deteriorated. No exercise measurement was performed despite being in the window of the 6-week visit. The LOCF value clearly does not reflect status at termination. Flolan was not started till after the 100-day window.
01:04/ 19005 ADR UT-15	This was a 63-year old female with PPH and NYHA Class III. The maximum dose received was 5.0 ng/kg/min. The subject discontinued study after approximately 9 weeks due to infusion site pain with no improvement in symptoms of pulmonary hypertension. The subject was alive 1-month post discontinuation. <table><tr><td>Day</td><td>1</td><td>10</td><td>45</td></tr><tr><td>Six minute walk in meters</td><td>264</td><td>276</td><td>180</td></tr><tr><td>Dyspnea fatigue index score</td><td>5</td><td>6</td><td>6</td></tr></table>	LOCF. Subject was censored on day 63. Flolan was started after the window of the study. The last exercise performance was two weeks prior to discontinuation.
01:04/ 19008 ADR UT-15	This was a 55-year old female with PPH and NYHA Class III symptoms. The maximum infusion the subject received was 5.0 ng/kg/min The subject discontinued after 6 weeks of therapy and was subsequently lost to follow up. Upon this reviewer's request, the subject was located. The sponsor claims the subject was doing well and not treated with Flolan.	LOCF. Assuming the sponsor is accurate, this subject could be censored. The was clearly no exercise benefit but a moderate worsening of the dyspnea fatigue index

Study Subject Class[90] Arm	Description	Classification by reviewer
	<table><tr><td>Day</td><td>1</td><td>12</td><td>45</td></tr><tr><td>Six minute walk in meters</td><td>315</td><td>343</td><td>355</td></tr><tr><td>Dyspnea fatigue index score</td><td>7</td><td>5</td><td>5</td></tr></table>	
01:05/ 19502 ADR UT-15	This was a 69-year old female with Class IV CHF secondary to pulmonary hypertension in association with scleroderma. The subject received a maximum dose of 1.3 ng/kg/min. The subject discontinued after approximately 5 weeks due to site pain. Approximately 1-month post study she started on Flolan. <table><tr><td>Day</td><td>1</td><td>8</td><td>45</td></tr><tr><td>Six minute walk in meters</td><td>186</td><td>207</td><td>241</td></tr><tr><td>Dyspnea fatigue index score</td><td>2</td><td>4</td><td>2</td></tr></table>	Worst outcome by analysis #2. Treated as worse outcome because of use of Flolan at approximately day 76.
01:05/ 52006 ADR Vehicle	This was a 46-year old female with NYHA Class III and PPH. This subject received vehicle at a maximum dose of 3.75 ng/kg/min. This subject was admitted to a hospital due to a viral infection. The subject subsequently died. <table><tr><td>Day</td><td>1/2</td><td>9</td></tr><tr><td>Six minute walk in meters</td><td>296</td><td>269</td></tr><tr><td>Dyspnea fatigue index score</td><td>3</td><td>3</td></tr></table>	Worst outcome by Analysis #1. This subject is classified as an ADR but is clearly a worst outcome secondary to death.
01:05/ 52008 ADR UT-15	This was a 37-year old female with a history of primary pulmonary hypertension and NYHA Class III status. The maximum dose of UT-15 was 2.5 ng/kg/min. UT-15 infusion was stopped after 47 days due to infusion site pain and the subject was immediately started on Flolan. <table><tr><td>Day</td><td>2</td><td>9</td></tr><tr><td>Six minute walk in meters</td><td>260</td><td>273</td></tr><tr><td>Dyspnea fatigue index score</td><td>2</td><td>2</td></tr></table>	Worst outcome by analysis #2. Flolan started within 100 day time window of study. Although an exercise test should have been scheduled at the time of discontinuation, none was performed. The subject was transplanted four months later (post window of study). A LOCF analysis clearly optimistically treats this subject's outcome
01:05/ 54011 ADR UT-15	This was a 54-year old female with a history of pulmonary hypertension and Eisenmengers syndrome. The maximum dose was titrated to 2.5 ng/kg/min but terminated infusion on approximately day 31. The subject was alive one-month post discontinuation. The subject did not receive Flolan. <table><tr><td>Day</td><td>0</td><td>8/9</td></tr><tr><td>Six minute walk in meters</td><td>288</td><td>235</td></tr><tr><td>Dyspnea fatigue index score</td><td>3</td><td>6</td></tr></table>	Censored at day 31.
01:05/ 54012 ADR UT-15	This was a 62-year old female with a history of PPH and NYHA Class III status. The subject was stared on UT-15 and received a maximum dose of 2.5 ng/kg/min After approximately 1 week at this dose (day 16) the subject discontinued from the study due to infusion site pain. The subject started flolan "electively" five days later. <table><tr><td>Day</td><td>1</td><td>9/10</td></tr><tr><td>Six minute walk in meters</td><td>233</td><td>275</td></tr><tr><td>Dyspnea fatigue index score</td><td>3</td><td>3</td></tr></table>	Worst outcome by analysis # 2. Due to inception of Flolan treatment.
01:05/ 54018 ADR UT-15	This was a 43-year old female with PPH and NYHA Class III. The subject received a maximum infusion rate of 3.75 ng/kg/min The subject discontinued on day 48 because of infusion site pain. Prior to final termination of UT-15, the subject was hospitalized to start Flolan infusion.	Worst outcome by analysis #2. Treated as worst outcome. Flolan started during course of study.

Study Subject Class[90] Arm	Description	Classification by reviewer
	Day: 2 / 8/11 / 43/47 Six minute walk in meters: 335 / 380 / 325 Dyspnea fatigue index score: 3 / 11 / 6	
01:05/ 60005 WC UT-15	This was a 43 -year old female with primary pulmonary hypertension and NYHA Class III, who was discontinued from the study on day 38 of therapy with the final down titration on day 46 because of hemolytic anemia. The subject was alive 30 days later with no comment on whether this subject required inotropic or Flolan support during the on-going duration of study. Day: -2/0 / 8/9 / 44 / 87 Six minute walk in meters: 425 / 475 / 225 / 340 Dyspnea fatigue index score: 6 / 5 / — / —	Censored LOCF day 44 measurement.
01:05/ 60007 WC UT-15	This was 67-year old female with primary pulmonary hypertension and NYHA Class III status. The subject received UT-15 for a total of 16 days when she was requested withdrawal from the study. The subject was alive at 1-month post discontinuation. No information is supplied if the subject was alive at 100 days after the inception of therapy and whether the subject required inotropic or flolan support during the study duration Day: -1 / 9 Six minute walk in meters: 357 / 439 Dyspnea fatigue index score: 5 / 5	Censored LOCF. Poor follow-up, taking a more lenient position this subject was considered as censored in day 16

There were a total of 19 UT-15 subjects who discontinued due to ADRs these 18 had at least one post-baseline measurement. There were in addition two subjects who discontinued due to withdrawal of consent. One subject had no post-baseline measurement and nine subjects had no week 6 measurement. Values for these nine subjects were imputed for the 6-week visit.

Reviewer's analysis #1

This was similar to the pivotal analysis mITT population, using a non-parametric method. Those who died, or were transplanted during the 100-day window of the study were treated as a worse outcome. There were five such subjects in the database [#4503 (UT-15), #10507 (UT-15), #58001 (UT-15), #16006 (vehicle), #52006 (vehicle)]. One vehicle subject (#16006) although completed the study was unable to walk at final visit and was assigned a walking distance of 0 feet. The p-value for treating these patients as worst outcome is shown in Table 62. The p-values for the individual studies was > 0.1. The p-value for the pooled study was 0.02.

Table 62. Results of reviewer's analysis #1[91] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.10	0.10	0.02

Reviewer's analysis #2

[91] *Nominal p-values include deaths and transplantation within the 100-day, mITT cohort, non-parametric analysis.*

This analysis treated those who died, received transplantation within 100 days or were started on Flolan within 1 month of discontinuation as worst outcomes. Those subjects who were treated with flolan within 30 days of discontinuation (the time of flolan inception) are [#54018 (before discontinuation of UT-15); #52008 (immediately upon discontinuation of UT-15); #54012 (5 days post UT-15); #2006 (2 weeks post UT-15); #2020 (1 month post UT-15); #19502 (1 month post UT-15)]. The p-values are shown below. To the extent that some of those who started on Flolan had not decompensated but were started on treatment due to no viable alternative to therapy, this analysis unduly penalizes active treatment.

Table 63. Results of reviewer's analysis #2[92] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.23	0.22	0.08

The result of this analysis even suggests the pooled data is no longer statistically significant. Each of the individual studies is far from significant.

Reviewer's analysis # 3

This analysis treated those who died, received transplantation or received Flolan during the window of the study or whose course was clearly downhill were treated as worse outcomes. This includes patient [#2001 (6-weeks); #11002 (2 months)] ; #5009 (markedly worse dyspnea/fatigue index). In addition, subject # 2016 this subject had an LOCF value based on week 1 measurements that was increased over baseline by 208 meters, yet upon discontinuation on day 47, this patient had evidence of shortness of breath. The LOCF value clearly does not reflect the value at the end of the study. This subject's value should be censored with no LOCF. The results are shown below. To the extent that some of those who started on flolan had not decompensated but were started on treatment due to no viable alternative to therapy, this analysis unduly penalizes active treatment.

Table 64. Results of reviewer's analysis #3[93] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.27	0.22	0.11

There are other subjects whose histories suggest a worse performance at the time of discontinuation but did not fit into the three categories that formed the three analyses. Additional analyses could incorporate these subjects as worse outcomes. There are also subjects who discontinued treatment during the time window appropriate for the six-week exercise test. The test, however, was not performed prior to discontinuation. There was one additional subject who was apparently lost to follow-up. The status of this subject during the 12-week study period is unclear. Treating all these subjects as worst outcomes could have been rationalized, further degrading any p-value estimate.

Bias from concurrent medication. There is a second set of biases that resulted from the asymmetry of infusion site pain. Subjects treated with UT-15 were more likely treated with opiate agonists, anti-inflammatory drugs or other medications than were vehicle subjects. It is not inconceivable that these medications may have hemodynamic

[92] *Nominal p-values include deaths and transplantation within the 100-day window as well as those treated with Flolan within 30-days of discontinuation as worse outcome, mITT cohort, non-parametric analysis.*

[93] *Nominal p-values include patients who died or were transplanted as well as those treated with Flolan within the 100-day window, mITT cohort, non-parametric analysis.*

effects on their own. The sponsor has submitted the following analyses to answer the question of the independent effect of opiates and anti-inflammatory drugs.

Table 65. Effect of opiates and anti-inflammatory drugs on walking distance (P01:04-05)

		Type of Analysis			
		No imputation		Imputation	
		No Drug	Yes Drug	No Drug	Yes Drug
Opiates	N	148	53	168	64
	Mean±SE	23±5	1±8	3±8	-14±14
Anti-inflammatory	N	121	80	134	98
	Mean±SE	21±6	11±6	1±9	-7±10
Any pain medication	N	55	146	64	168
	Mean±SE	22±11	15±5	-11±16	2±7

Those who need pain medication, either opiates, anti-inflammatory or any generally performed better than those who required none for the no-imputation analysis. The process of imputation has a slightly lesser effect on the subjects who received pain medications. For example imputing data for those who did not complete the study decreased the estimated 6-minute walk distance for those with any pain medication by 33 meters. For those who received some sort of pain medication the imputed value dropped by only 13 meters. The variability of the measurements, however, makes any conclusion highly speculative. There is, therefore, no convincing evidence that pain medication alters the 6-minute walk distance.

Sponsor's analysis at week 1 and 6

The sponsor's analysis shows minimal additional increase in 6-minute walk for the UT-15 group after week 1. The vehicle group, however, shows a gradual decline in the 6-minute walk distance at weeks 6 and 12, but at all points appears to be no worse than baseline. The net-difference between UT-15 and vehicle over time shows a small increase in walk distance.

The dose of UT-15 during this period of time was 1.2 ng/kg/min at week 1, 5.9 ng/kg/min at week 6 and 9.2 ng/kg/min at the end of week 12. The initial dose was predicated on having minimal activity. It is therefore, somewhat surprising that despite a nearly 8-fold increase in dose, there was little additional benefit in walking distance. The splaying of the difference between treatment and vehicle may in part or in total reflect the process of imputation as oppose to a real effect on walking distance.

Table 66. Sponsor's analysis of 6-min walk at weeks 1-12 (P01:04-05)[94]

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Week 1	N	110	106	121	118	231	224
	Median	0	12	12	11	8	11
	25th-75th %ile	-17, 26	-9, 31	-9, 35	-9, 29	-12, 32	-9, 32
	P-value		0.22		0.86		0.27
Week 6	N	111	113	125	119	236	232
	Median	0	9	7	15	5	13
	25th-75th %ile	-38, 24	-20, 38	-23, 39	-21, 48	-29, 34	-20, 45
	P-value		0.16		0.14		0.03
Week 12	N	111	113	125	119	236	232
	Median	1	3	-3	16	0	10
	25th-75th %ile	-53, -31	-27, 67	-37, -35	-22, 37	-45, -33	-25, -48
	P-value		0.06		0.55		0.06

FDA statistician's analysis of time course

A linear mixed effect model was used as an exploratory analysis to define the treatment effects with respect to time dependent and disease etiology-dependent effects of treatment. The model assumes those who discontinued early, regardless of the reason, would have walked distances similar to those who completed. The model includes a quadratic term for time. Other parameters used in constructing the model include: treatment group, baseline distance walked, etiology, vasodilator use in the primary pulmonary hypertension subjects. The statistician's curves are shown in Figure 13.

This analysis shows all groups had an increase in walk distance at the 1-week (approximately day 7) measurement. There was a greater benefit initially among all subjects independent of disease etiology that was treated with UT-15 than vehicle. There was little alteration in effect at week 6 (approximately day 42). The major difference in outcome occurs at the end of the study measurement. The UT-15 group splays upward, the vehicle group splays downward. Since those who prematurely discontinued were presumed to maintain their rank at the last measurement, some component of the splay may be related to the asymmetry in discontinuations. There were nine subjects imputed values at week 6. Eighteen of the 19 subjects that had adverse event dropped out had values imputed for the week 12 measurement. The last subject #7004 who discontinued on day 25, nevertheless had a 12-week measurement performed off treatment. This value was used for this patient.

[94] *Derived from sponsor's table 11.4.1.1.4H; summary of change from baseline in six-minute walk test at Weeks 1, 6, and 12; non-parametric analysis of mITT group*

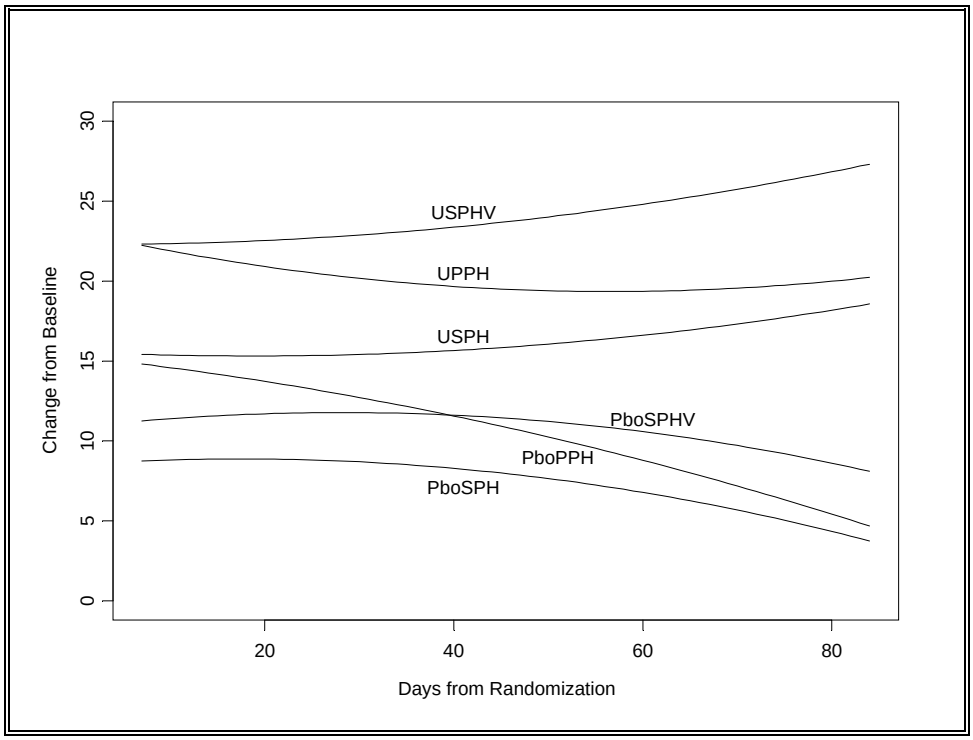


Figure 13. FDA statistician's analysis of time course (P01:04-05)
Fitted curves from linear mixed effects model at the average baseline value. USPHV=Uniprost, secondary PH, vasodilator use; VehiclePPH=Vehicle, PPH, etc.

Effect of baseline walking distance. The sponsor's Integrated Summary of Efficacy contains an analysis[95] suggestive that the effect of treatment with UT-15 was greater among subjects who were less able to walk at baseline. That analysis divided the population into quarters of the observed range of baseline walking distance (rather than quartiles of subjects). Estimates of the treatment effect in these subgroups are shown in Table 67.

Table 67. Treatment effect on walking distance by baseline distance (P01:04-05).

Baseline	UT15-Vehicle mean±SE	P-value
<150 m	51±16	0.0019
150 - 250 m	33±10	0.0005
250-350 m	16±7	0.03
>350 m	-2±12	0.87

As part of this review, the 416 subjects with both baseline and week 12 data (i.e., without imputation) were identified and the magnitude of treatment effect[96] was computed for successive blocks of 10 subjects, from the lowest baseline to the highest baseline value, using a moving bin technique. The results are shown in Figure 14.

[95] *Sponsor's Integrated Summary of Efficacy, Table 8.7.7B on page 140.*

[96] *{Dist(UT-15, Week 12) - Dist(UT-15, Baseline) } - { Dist(Veh, Week 12) - Dist(Veh, Baseline) }*

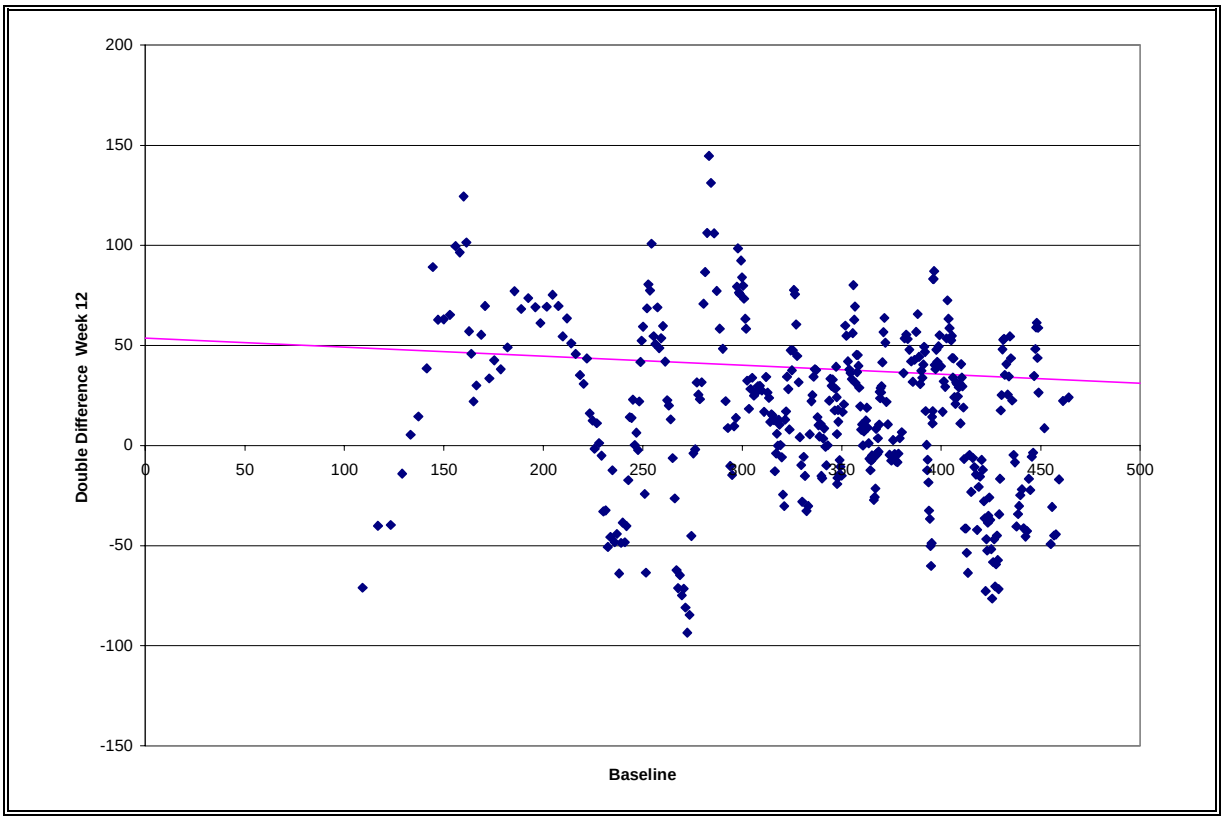


Figure 14. Moving-bin estimate of treatment effect on walking distance (m) at week 12 (P01:04-05)

Analysis described in text. The line is a linear least-sqaures line fit using JMP. The fitted line has intercept 176±28 feet and slope -0.111±0.025 , both significantly different from zero ($p < 0.0001$). The correlation coefficient, r^2, was 0.05.

This analysis is weakly supportive that the treatment effect is larger in subjects with lower baseline walking distances.

A.4.4.7.2 Secondary outcome measures

Signs and symptoms of PAH.

Table 51 shows the 16 signs and symptoms that were assessed. Subjects may or may not have had abnormalities or they may not have been asked about that particular sign or symptom at baseline or at subsequent visits. Each of these signs and symptoms were graded as shown in Table 68.

Table 68. Grading of signs and symptoms (P01:04-05)

Sign/Symptom	Grades
Fatigue	+1 to + 4
Dyspnea	Mild to moderate exertional dyspnea Paroxysmal nocturnal dyspnea Increasing exertional dyspnea Nocturnal cough/ Dyspnea at rest
Orthopnea	1 pillow 2 pillows 3 pillows Bed on blocks Sleeps in chair
Jugular venous distention	0 to ≤ 6 cm > 6 cm
Edema	Feet and ankles Lower legs and thighs Sacrum
Syncope	Some of the time Most of the time All of the time
Dizziness	
Palpitations	
Chest pain	
Loud P2 sound	No grades
Third heart sound	
Fourth heart sound	
Right ventricular heave	
Systolic murmur	Grade 1-6
Diastolic murmur	
Herpatomegaly	0-3 below RCM > 3 and < 6 below RCM

Despite the grading system, the value of each symptom was collapsed into a single metric. A ”+1” was assigned for any sign that was present at baseline but absent at 12-week evaluation, and “–1” for any sign that was absent at baseline but present at baseline and a “0” for each sign and symptom that was present or absent at both time points. The overall change in score was the sum of these values over all signs and symptoms, provided at least eight of these 16 signs were assessed both at baseline and follow up. Subjects who did not complete the study were censored at the time of discontinuation.

The specifics at baseline of the signs and symptoms of pulmonary hypertension are shown in Table 69. There were somewhat more subjects with right ventricular heave and edema in the vehicle group and more subjects with dizziness and palpitations in the UT-15 group.

Table 69. Signs and symptoms at baseline (P01:04-05)[97]

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Dyspnea	109 (98)	113 (100)	125 (100)	120 (100)	234 (99)	233 (100)
Loud P2	109 (98)	109 (97)	117 (94)	111 (93)	226 (96)	220 (94)
Fatigue	97 (87)	106 (94)	107 (86)	105 (88)	204 (96)	211 (91)
Systolic murmur	80 (72)	77 (68)	71 (57)	70 (58)	151 (64)	147 (63)
Right ventricular heave	83 (75)	79 (70)	63 (50)	53 (44)	146 (62)	132 (57)
Jugular venous distension	61 (55)	68 (60)	71 (57)	64 (53)	132 (56)	132 (57)
Dizziness	54 (49)	58 (51)	53 (42)	64 (53)	107 (45)	120 (52)
Palpitations	50 (45)	60 (53)	50 (40)	61 (51)	100 (42)	121 (52)
Edema	53 (48)	52 (44)	58 (46)	44 (37)	111 (47)	96 (41)
Chest pain	43 (39)	46 (41)	48 (39)	49 (41)	91 (39)	95 (41)
Orthopnea	35 (32)	44 (39)	38 (30)	32 (27)	73 (31)	76 (33)
Hepatomegaly	22 (20)	24 (21)	35 (28)	29 (24)	57 (24)	53 (23)
Fourth heart sound	36 (32)	34 (30)	24 (19)	20 (17)	60 (25)	54 (23)
Third heart sound	14 (13)	15 (13)	21 (17)	15 (13)	35 (15)	30 (13)
Diastolic murmur	18 (16)	14 (12)	11 (9)	12 (10)	29 (12)	29 (12)
Syncope	7 (6)	13 (12)	10 (8)	7 (6)	17 (7)	20 (9)

Nearly all subjects had had dyspnea, and fatigue as the most common symptom. A loud P2 sound was the most frequent sign. The groups were relatively well balanced, although right ventricular heave and edema were more frequent in the vehicle group. Dizziness and palpitations were more frequent in the UT-15 group.

Sponsor's analysis. There are no data submitted as to the average number of signs and symptoms per subject at baseline. Consequently, the change in baseline signs and symptoms of PAH cannot easily be understood. Scores could range from –16 for a subject that had symptoms at baseline for each component to –1 for someone who had only one symptom. The analysis presumes that subject's are balanced at baseline.

Table 70. Change in signs and symptoms score (P01:04-05)[98]

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Week 1	N	110	111	123	119	233	230
	Change	0.7±0.2	0.9±0.2	0.5±0.1	0.8±0.2	0.6±0.1	0.8±0.1
	P-value	0.72		0.19		0.25	
Week 6	N	107	107	120	109	227	216
	Change	0.4±0.2	1.2±0.2	0.3±0.2	0.8±0.2	0.3±0.1	1.0±
	P-value	0.02		0.12		0.005	
Week 12	N	103	97	114	104	217	201
	Change	-0.1±0.2	0.9±0.3	0.0±0.2	1.0±0.2	-0.1±0.2	0.9±0.2
	P-value	0.01		<0.001		<0.001	

The data above demonstrate a benefit in the treatment group relative to vehicle at week 6 and 12. A more careful view of the data show that the effect on symptoms for the UT-15 group shows that maximal effect was seen at week1. The attainment of statistical significance more reflects deterioration in the relative status of the vehicle group.

[97] *Data from sponsor's table 11.2.2.5.*

[98] *mITT group; from sponsor's table 11.4.1.2.1A.*

Comment. The data first should be interpreted in the context of who assigned values. In this case the treating physician based on interviews with the subject completed the dyspnea-fatigue index. It is this reviewer's impression that the treating physician was likely aware as to the treatment group based on the presence of severe infusion site pain. The assignment of values is likely to be subjectively confounded by knowledge of therapy.

There are several ways to interpret the above study. The sponsor's analysis would suggest that there is a persistent benefit to UT-15 therapy. There was however, a large drop out preferentially in the UT-15 group. An alternative interpretation to the data would be that there was a differential dropout was due to worsening in signs and symptoms in that population who discontinued. As a thought experiment, if the 33 subjects who were enrolled who did not contribute to the 12-week measurement had an average score of "–3 to -4", that is three or four of the sixteen metrics were worse at week 12 in these dropouts. The net effect would disappear. This sort of analysis is clearly an over correction since it assumes no vehicle subject including patients who died had such values imputed.

There is, therefore, probably some signal here; the magnitude, however, is unclear.

A shift table on the individual signs and symptoms that contributed to the dyspnea fatigue index is shown below. The symptoms that improved are dizziness, palpitations, chest pain and orthopnea. Of note there was no convincing benefit to the UT-15 for the three most common signs and symptoms of pulmonary hypertension i.e. dyspnea, fatigue and loud P2. Other metrics (See under Dyspnea-fatigue index and Borg index), however, appears compatible with an improvement in the most bothersome symptoms of pulmonary hypertension.

Table 71. Subjects with baseline symptoms improved or worsened (P01:04-05)[99]

		Improved			Worsened		
		Veh	**UT-15**	**P-value**	**Veh**	**UT-15**	**P-value**
Dyspnea	Pooled	4 (2)	8 (3)	0.25	1 (0)	0 (0)	>0.99
	P01:04	0 (0)	1 (1)		1 (1)	0 (0)	
	P01:05	4 (3)	7 (6)		0 (0)	0 (0)	
Loud P2 sound	Pooled	5 (2)	7 (3)	0.56	8 (3)	7 (3)	>0.99
	P01:04	2 (2)	4 (4)		1 (1)	3 (3)	
	P01:05	3 (2)	3 (3)		7 (6)	4 (3)	
Fatigue	Pooled	12 (5)	17 (7)	0.25	12 (5)	5 (2)	0.14
	P01:04	5 (5)	9 (8)		4 (4)	2 (2)	
	P01:05	4 (6)	8 (7)		8 (6)	3 (3)	
Systolic murmur	Pooled	15 (6)	10 (4)	0.42	19 (8)	19 (8)	0.87
	P01:04	11 (6)	7 (6)		13 (12)	11 (11)	
	P01:05	3 (6)	3 (3)		6 (5)	8 (6)	
Right ventricular heave	Pooled	14 (6)	20 (9)	0.28	25 (11)	25 (11)	0.76
	P01:04	11 (10)	12 (11)		16 (14)	17 (15)	
	P01:05	3 (2)	8 (7)		9 (7)	8 (7)	
Jugular venous distension	Pooled	21 (9)	33 (14)	0.06	30 (13)	19 (8)	0.17
	P01:04	11 (10)	15 (13)		17 (15)	11 (10)	
	P01:05	10 (8)	18 (15)		13 (10.)	8 (7)	
Dizziness	Pooled	35 (15)	55 (24)	0.006	33 (14)	27 (12)	0.68
	P01:04	20 (18)	25 (22)		18 (16)	18 (16)	
	P01:05	15 (12)	30 (25)		15 (12)	9 (8)	
Palpitations	Pooled	25 (11)	46 (20)	0.003	22 (9)	27 (12)	0.36
	P01:04	10 (9)	21 (19)		9 (8)	13 (16)	
	P01:05	15 (12)	25 (21)		13 (10)	14 (12)	
Edema	Pooled	23 (10)	36 (16)	0.04	29 (12)	18 (8)	0.17
	P01:04	13 (12)	18 (16)		13 (12)	16 (14)	
	P01:05	10 (8)	18 (15)		16 (13)	2 (2)	
Chest Pain	Pooled	37 (16)	48 (21)	0.09	30 (13)	8 (3)	0.0005
	P01:04	15 (14)	26 (23)		15 (14)	5 (4)	
	P01:05	22 (18)	22 (18)		15 (11)	3 (3)	
Orthopnea	Pooled	14 (6)	29 (12)	0.01	30 (13)	17 (7)	0.09
	P01:04	7 (6)	19 (17)		16 (14.)	10 (9)	
	P01:05	7 (6)	10 (8)		14 (11)	7 (12)	
Hepatomegaly	Pooled	18 (8)	26 (11)	0.15	18 (8)	11 (5)	0.34
	P01:04	9 (8)	16 (14)		7 (6)	7 (6)	
	P01:05	9 (7)	10 (8)		11 (9)	4 (3)	
Fourth heart sound	Pooled	24 (10)	14 (6)	0.17	26 (11)	19 (8)	0.43
	P01:04	13 (11)	9 (8)		14 (13)	12 (11)	
	P01:05	11 (9)	5 (4)		12 (10)	7 (6)	
Third heart sound	Pooled	15 (6.)	7 (3)	0.19	12 (5)	12 (5)	>0.99
	P01:04	6 (5)	4 (4)		5 (5)	6 (5)	
	P01:05	9 (7)	3 (3)		7 (6)	6 (5)	
Diastolic murmur	Pooled	8 (3)	5 (2)	0.58	10 ()	4 (2)	0.18
	P01:04	6 (5)	4 (4)		5 (5)	2 (2)	
	P01:05	2 (2)	1 (1)		5 (4)	2 (2)	
Syncope	Pooled	10 (4)	15 (6)	0.30	7 (3)	1 (0)	0.07
	P01:04	4 (4)	8 (7)		2 (2)	1 (1)	
	P01:05	6 (5)	7 (6)		5 (4)	0 (0.)	

[99] *Based on sponsor's Table 11.4.1.2.1C and 11.4.1.2.1D. P-value from Fisher's exact test. P-values not corrected for multiple comparisons.*

The percentages of improved or worsened reflect those who improved relative to the total number of subjects at baseline. The true metric should be based on those with the symptom at baseline. Subjects who discontinued for adverse events were censored. The percentage for those that worsened could therefore be higher.

There are some suggestions from the data that UT-15 may alter some symptoms such as chest pain, palpitation, dizziness and edema. The more frequent and bothersome symptom of dyspnea and fatigue do not apparently change with UT-15 infusion. Some of the symptoms lack specificity in their description. Was the chest pain cardiac in nature? Others symptoms that improved may overlap and are therefore double-counted i.e. were palpitations and dizziness independent symptoms.

It is difficult to amalgamate the entirety of these symptoms into an overall benefit. No global question was asked "Are you feeling better or worse since you enrolled?". The sponsor's attempted to conglomerate the sum of the symptoms by summing all better or worse outcomes for the 16 symptoms. This analysis weighs all symptoms the equivalently. There are clearly more pertinent and disease related symptoms than others. In particular, dyspnea and fatigue were apparently not altered.

Some additional comments are appropriate. Week 12 data were predicated on censoring of subjects. The fact that subjects who discontinued did not have their symptoms assessed, biases the results towards UT-15 in allowing fewer subjects to potentially worsen. Conversely, it biases against improvement since fewer subjects are potentially available for improvement. This analysis assumes that any negative effect on symptoms at the time of discontinuation was not pertinent to the decision to discontinue. This is clearly an invalidated assumption.

There are clearly additional problems with this set of data. The physician, who was aware of the presence and intensity of infusion-site pain, completed the symptom assessment. Since infusion pain was so much more common in the treatment group, there may have been subtle bias in the assessment of this pain.

The overall pattern of symptom benefit is perplexing. If the mechanism of action of UT-15 is to decrease pulmonary artery resistance and pulmonary artery pressures, the particular benefit should be on hepatomegaly, ascites and edema. In fact more subjects on UT-15 reported edema as an adverse event than vehicle subjects (9% versus 3%). If the drug were particularly effective, then dyspnea and fatigue should also be affected. None of these parameters were convincingly altered.

On the other hand it is unclear how mechanistically one would interpret a benefit on orthopnea. This symptom would in general be attributed to left-sided cardiac failure. Since those who enrolled were precluded from having left-sided cardiac disease, the origin of the orthopnea is unclear, consequently, the mechanism of benefit is unclear. The effect on chest pain could reflect a decrease on right-sided ischemia, but the description of chest pain is unclear

There was a clear imbalance in the use of pain medications. More UT-15 subjects, because of infusion site pain, were taking opiates and/ or anti-inflammatory drugs than vehicle subjects. The sponsor compared the effect on symptoms of those who were treated with opiates to those who were not so treated. The sponsor found no statistical difference between those who were treated with opiates and those who were not. Any effect of opiate antagonists on signs and symptoms may exist but is small.

Dyspnea Fatigue Index

The dyspnea fatigue rating scale consists of three categories of performance (see Table 1.7). The metrics defines the magnitude of the task, the magnitude of the pace and the functional impairment of the subject. Each category contains 5 possible values that ranging from 4 to 0, with 4 indicating minimal compromise and 0 severe compromise.

The treating physician based on the subject's report completed the dyspnea-fatigue questionnaire.

The analysis below is based on only the actual data. There was no imputation of values for those who discontinued for death, deterioration or transplant. Missing values for those who discontinued for adverse events were also not imputed.

Table 72. Change in dyspnea-fatigue index (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Baseline		4.7±2.0	4.3±2.0	4.2±2.0	4.2±1.9	4.4±2.0	4.3±1.9
Week 1	N	110	111	123	118	233	229
	Change	0.1±1.4	0.2±1.6	-0.1±0.9	0.2±1.0	0.0±1.1	0.2±1.2
	P-value	0.4		0.01		0.02	
Week 6	N	107	108	120	110	227	218
	Change	0.1±1.8	0.9±1.9	0.3±1.5	0.7±1.7	0.2±1.6	0.8±1.8
	P-value	0.002		0.02		0.0001	
Week 12	N	102	97	114	104	216	97
	Change	-0.2±2.1	0.8±1.8	-0.1±1.6	1.3±2.0	-0.1±1.8	0.8±1.8
	P-value	0.002		<0.0001		<0.0001	

The effect of UT-15 on the components of the Dyspnea-Fatigue rating for the pooled data base show an improvement in all three categories, i.e. magnitude of the task, magnitude of the pace and functional impairment, as shown in Table 73.

Table 73. Effect of treatment on components of the dyspnea fatigue index (P01:04-05)

	Level	Baseline		Week 12	
		Veh N=236	UT-15 N=233	Veh N=216	UT-15 N=201
Magnitude of task	0	8	10	11	6
	1	109	111	96	48
	2	107	105	92	112
	3	10	7	15	34
	4	2	0	2	1
	Average	1.53	1.47	1.54	1.88
Magnitude of pace	0	10	8	10	5
	1	103	119	99	50
	2	109	92	88	108
	3	12	14	18	38
	4	2	0	1	0
	Average	1.55	1.48	1.54	1.89
Functional impairment	0	43	46	47	21
	1	90	88	78	59
	2	84	83	74	86
	3	16	15	15	33
	4	3	1	2	2
	Average	1.35	1.30	1.29	1.68

The pooled data indicate that there is an improvement of approximately 0.38-0.41 units for each of the components of the dyspnea fatigue index for the treatment group. For the vehicle group there was minimal effect on the magnitude of task and magnitude of pace of task, there was, however some deterioration in the functional impairment in the vehicle group. The results would suggest approximately 1/3 of the subjects had a unit change in each of the components.

There were more subjects who discontinued in the UT-15 group than in the vehicle group. Assuming all such subjects received a "0" for each component, and the vehicle subjects who discontinued were censored, the magnitude of the effect would be only 0.18 units for the sum of the three components of the metric.

Quality of life

The Quality of Life (QOL) questionnaire was administered at baseline, week 6 and end of week 12. The specifics of the QOL questionnaire are shown in Section A.4.3.8 which begins on page 89. The QOL is divided into four components. The sponsor's chooses to analyze only three of these components. The questionnaire was not validated for a pulmonary hypertension population.

In this study the population for which data was available was a truncated population. At baseline only 371 of the 469 enrolled subjects had available data. At the 12-week time, the number of subjects was only 325. Not all subjects who completed the study were queried with respect to this questionnaire. Those who discontinued for adverse events as well as those who died, deteriorated or were transplanted were also not analyzed. The global QOL was no different between treatments. Only the physical dimension at the 12-week time study point nominally differed between the two treatments, as shown in Table 74.

Table 74. Quality of life assessments (P01:04-05)[100]

			P01:04		P01:05		Pooled	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
Global	Baseline	N	71	76	113	111	184	187
		Mean±SE	56.5±2.6	54.9±2.6	53.4±2.0	52.7±2.0	54.6±1.6	53.6±1.6
	Week 6	N	67	69	112	93	179	162
		Change	-5.1±2.1	-3.7±2.7	-5.8±1.6	-6.9±1.9	-5.5±1.3	-5.5±1.6
	Week 12	N	69	65	104	92	173	157
		Change	-1.2±2.3	-5.0±2.5	-2.9±1.9	-7.7±2.1	-1.9±1.4	-6.6±1.6
Physical	Baseline	N	71	76	113	111	184	187
		Mean±SE	25.6±1.1	25.5±1.1	25.2±0.9	24.4±0.8	25.4±0.7	24.9±0.7
	Week 6	N	67	69	112	93	179	162
		Change	-2.9±1.0	-3.5±1.2	-2.5±0.8	-3.7±0.8	-2.6±0.6	-3.6±0.7
	Week 12	N	69	65	104	92	173	157
		Change	-1.4±1.1	-4.3±1.2	-2.2±0.9	-4.7±0.9	-1.9±1.4	-4.5±0.7
Emotional	Baseline	N	71	76	113	111	184	187
		Mean±SE	13.5±0.8	12.8±0.9	11.4±0.7	11.6±0.7	12.2±0.5	12.1±0.6
	Week 6	N	67	69	112	93	179	162
		Change	-1.5±0.7	-0.5±0.9	-1.5±0.5	-1.9±0.6	-1.5±0.4	-1.3±0.5
	Week 12	N	69	65	104	92	173	157
		Change	-0.8±0.7	-1.1±0.7	-0.2±0.6	-1.5±0.6	-0.3±0.5	-1.3±0.5

Borg Dyspnea Score

This metric was not part of the pivotal measurements. The Borg-Dyspnea scale was administered immediately after each of the exercise tests. The instructions are described on page 94.

[100] *Mean ± SE; from sponsor listing 14.2.9.2A-C.*

Table 75. Borg Dyspnea score (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	**UT-15**	**Veh**	**UT-15**	**Veh**	**UT-15**
Baseline	N	111	113	123	119	234	232
	Mean±SE	4.3±0.2	4.4±0.2	4.4±0.2	4.2±0.2	4.4±0.2	4.4±0.2
Week 1	N	106	105	118	116	226	221
	Change	-0.2±0.2	-0.4±0.1	0.1±0.2	-0.1±0.1	-0.1±0.1	-0.3±0.1
Week 6	N	106	104	113	109	219	213
	Change	0.1±0.2	-0.9±0.2	-0.1±0.2	-0.5±0.2	-0.2±0.1	-0.7±0.1
Week 12	N	99	97	108	103	207	200
	Change	0.0±0.2	-0.9±0.2	-0.2±0.2	-1.0±0.2	-0.1±0.1	-0.9±0.1

The comparison of the treatment groups at 12 weeks had a nominal p-value < 0.01 for the individual studies and the pooled studies. There was a benefit in Borg dyspnea scale. The pooled study shows a decrease in subjective symptoms of approximately 0.81 units.

Hemodynamics

Hemodynamic parameters were collected at baseline and at end of study. Table 76 lists the baseline value as well as the change from baseline for hemodynamic parameters for the pooled studies. The individual studies are not shown but are substantially in the same direction. A scatter plot of baseline versus end of study for all hemodynamic parameters is shown as Figure 15.

Table 76. Hemodynamic results (P01:04-05)[101]

		Baseline		Week 12 change		
		Veh	**UT-15**	**Veh**	**UT-15**	**P-val**
Heart rate bpm	N mean±SE	234 82±1	228 82±1	215 -1±1	198 -1±1	0.5
Right atrial pressure mmHg	N mean±SE	231 10±0.4	228 10±0.4	211 1.4±0.3	195 -0.5±0.4	<0.001
Cardiac index L/min/m^2	N mean±SE	232 2.2±0.05	225 2.4±0.06	209 -0.1±0.04	194 0.1±0.04	<0.001
Stroke index L/beat/m^2	N mean±SE	231 28±0.7	222 30±0.9	208 -0.6±0.5	193 1.8±0.6	<0.001
Pulmonary systolic mmHg	N mean±SE	235 95±1.5	231 96±1.6	215 0.3±0.9	199 -2.7±0.8	0.02
Pulmonary diastolic mmHg	N mean±SE	235 40±0.8	231 43±1.0	215 0.6±0.6	199 -2.2±0.6	0.002
Pulmonary mean mmHg	N mean±SE	235 60±1.0	231 62±1.2	215 0.7±0.6	199 -2.3±0.5	<0.001
Pulm vasc resis index mmHg/L/min/m^2	N mean±SE	203 25±0.9	204 27±1.0	187 1.2±0.6	163 -3.5±0.6	<0.001
Pulmonary cap wedge mmHg	N mean±SE	225 9.3±0.2	217 9.5±0.2	199 0.9±0.4	175 -0.1±0.3	0.08
Systemic systolic mmHg	N mean±SE	234 121±1.3	230 119±1.1	214 -0.4±0.8	198 -2.3±1.1	0.08
Systemic diastolic mmHg	N mean±SE	234 74±0.8	230 72±0.9	214 -0.4±0.1	198 -1.8±0.9	0.06
Systemic mean mmHg	N mean±SE	234 91±0.9	229 90±0.9	211 -1.0±0.9	197 -1.7±0.9	0.1
Syst vasc resis index mmHg/L/min/m^2	N mean±SE	219 39±1.0	211 38±1.1	190 -0.8±0.9	175 -3.5±1.0	0.3
Mixed venous oxygen %	N mean±SE	215 60±0.8	215 62±0.7	182 -1.4±0.7	181 2.0±0.8	<0.001
Respiration rate min^{-1}	N mean±SE	227 19±0.3	225 19±0.3	205 -0.4±0.3	194 -0.6±0.3	<0.2

The table indicates that for this truncated population (i.e. completers), there were modest decreases in right atrial pressures, pulmonary artery pressures (mean, systolic and diastolic) and pulmonary vascular resistance. Cardiac index, stroke index and mixed venous oxygenation were increased.

[101] *The p-value is based on the treatment effect of the ANCOVA with baseline and treatment as the covariates.*

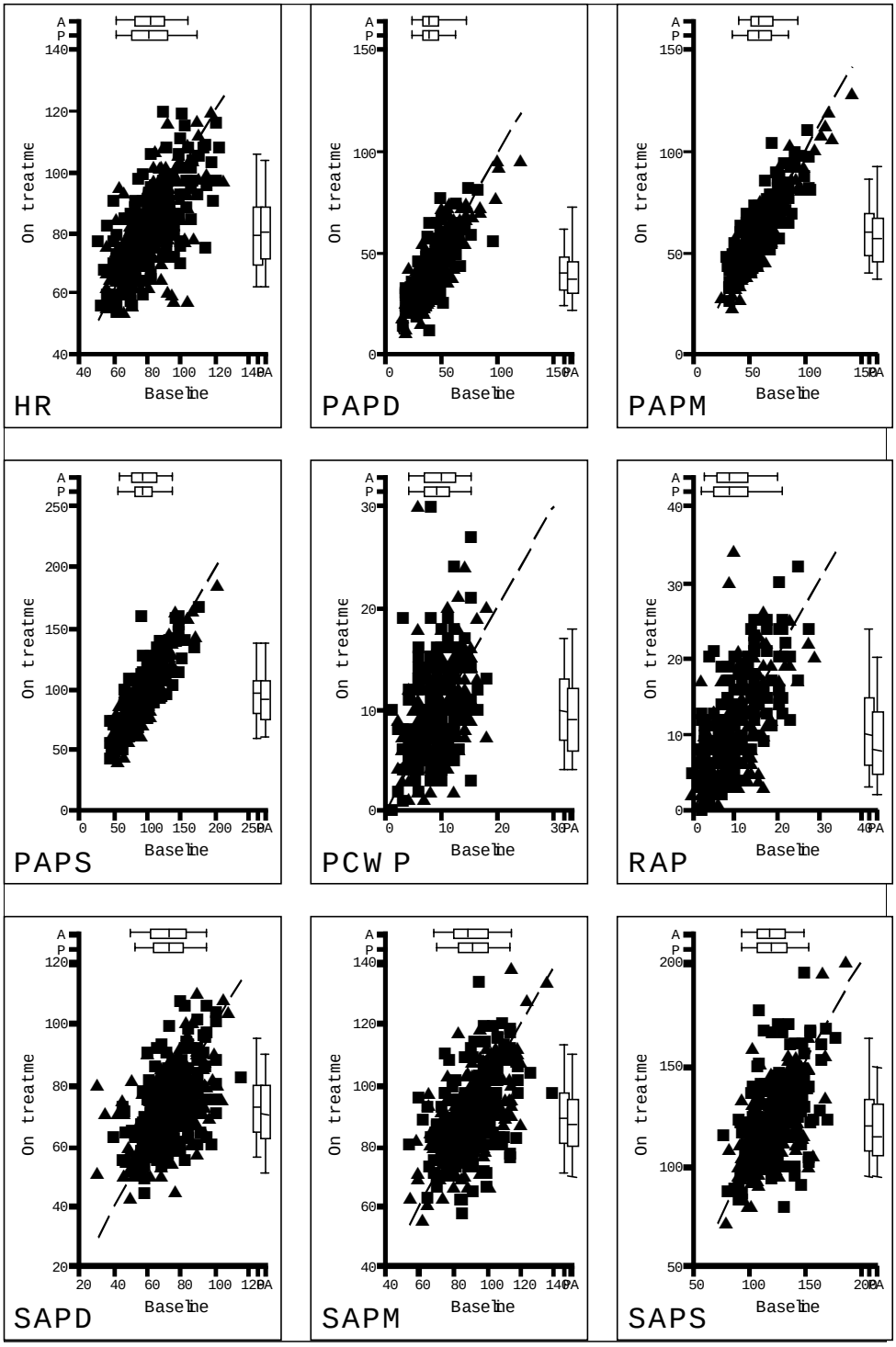


Figure 15. Hemodynamics scatter plots (P01:04-05)

Reviewers' analysis. Baseline and week-12 hemodynamic data are plotted for subjects on vehicle (P, square) and UT-15 (A, triangle). Marginal box-and-whiskers plots compare the distributions in the treatment groups at baseline and at 12 week.s. Panes are (HR) heart rate, (PAPD) pulmonary artery diastolic pressure, (PAPM) pulmonary artery mean pressure, (PAPS) pulmonary artery systolic pressure, (PCWP) pulmonary capillary wedge pressure, (RAP) right atrial pressure, (SAPD) systemic diastolic pressure, (SAPM) systemic mean pressure, and (SAPS) systemic systolic pressure.

The effect on hemodynamics, though statistically significant is in general small and of uncertain consequence. For cardiac index the net change (assuming that the data for those measured is consistent with the whole group) there was a net increase of 7.6%. There was an approximately 5% (3 mm Hg) decrease in mean pulmonary artery pressure. There was an approximately 18% decrease in pulmonary vascular resistance.

The sponsor was requested to analyze whether there was a correlation between hemodynamics (change in and % change in CI, PVR or PAPm) and walking distance, dyspnea fatigue rating or Borg-score. Among these 18 analyses only the correlation between PVR and walk distance was nominally significant (by Spearman-Rank correlation). Change in mixed venous oxygenation was correlated with walk and dyspnea fatigue index. The % change in mixed venous oxygenation was correlated with walk distance and dyspnea-fatigue index.

Oxygen saturation

Although prespecified as a secondary end-point, this metric was not measured. In fact it did not appear that this metric was collected. With the exception of those who were on oxygen, during catheterization, no oxygen saturation data was captured.

Other end points

The following end points are often considered in drugs for use in subjects with CHF due to left-sided systolic dysfunction. The outcomes would be reasonable to consider for subjects with pulmonary hypertension. They were not pre-specified as end-points for these studies.

Mortality

There did not appear to be a signal that mortality was altered by UT-15. There were a total of 19 subject who died during the course of the study. Nine in the UT-15 and ten in the vehicle group. Death occurred on treatment day (mean + SD) 42 $\pm$ 26 for UT-15 and on day 49 $\pm$ 35 for vehicle.

Of these deaths, six UT-15 (#4017, #9006, #10002, #23002, #51007, and #55005) and seven vehicle (#9012, #10001, #15003, #16003, #60006, #60015 and #65004) were listed as deaths. Four subjects, two in the UT-15 (subjects #54005 and #58001) and one vehicle subject (#65011) were listed as having deteriorated, these subjects died after the assessment of deterioration. There were two subjects, one UT-15 (#4503) and one vehicle (#52006) subject who were listed as adverse events who died. One subject in the vehicle group (#16006) was listed as having completed (the subject had the last cardiac catheterization) but died during the hospitalization.

Hospitalizations

This data was culled from Table 14.3.4.1, p 5609. That section of the submission contained narratives of all serious adverse events. These narratives should have captured all hospitalizations. There was no difference in the number of subjects hospitalized in comparing UT-15 to vehicle. There were 40 vehicle subjects and 38 UT-15 subjects who were hospitalized or had their duration of hospitalization increased. Capsular summaries for those hospitalized are available under safety. Two of the vehicle subjects who were hospitalized had actually inadvertently received UT-15 at the time of event that caused hospitalization.

With respect to the number of subjects who were hospitalized for cardiovascular events or worsening of pulmonary hypertension, any analysis would be highly subjective. This reviewer, however, counted those who died or appeared to be hospitalized for cardiovascular diseases as 25 in the vehicle group and 22 in the UT-15 group. Check marks next to the number in Table 82 on page 138 reflect this reviewer's judgement as to what was considered as a cardiovascular event.

Need for medication changes

With respect to subjects who required either pressor support or flolan, this reviewer counted 12 UT-15 subjects and 13 vehicle subjects who required pressors or flolan during the course of the study. Among those who were treated with pressors three vehicle subjects and no UT-15 subjects received flolan early on (day 2) of treatment for short duration (1 day). It seems that flolan in these subjects was used as a provocative test for pulmonary vascular responsiveness and not to treat worsening of status. Excluding these three subjects suggest 12 UT-15 and 10 vehicle subjects required inotropic or prostaglandin support during the study. There did not appear to be any differences in the need of pressors or flolan or pressors among the two treatments.

This reviewer also explored the need or increase of medications used for pulmonary hypertension. The data was contained in sponsor's Listing 16.2.4.7 of the NDA. This was not a pre-specified analysis, but has been used as support of medications that have been approved for the treatment of left-sided failure. Since this reviewer tabulated the data by hand and not by querying the database, the analysis is only be considered an approximation.

The metric used was the number of subjects who received treatment with an additional drug used to treat pulmonary hypertension or had one of these ongoing medications increased at the end of treatment relative to baseline. The drug classes that were considered in this analysis were those that might be increased in subjects whose pulmonary hypertension status was worsening. The drugs included loop diuretics, calcium channel blockers, vasodilators (including hydralazine, clonidine, nitrates), ACE inhibitors or angiotensin II blockers, oxygen, flolan, pressors, steroids, digoxin, aldactone or non-loop diuretics. Topical steroids used for the treatment of infusion site pain were not included in the sponsor's listing but captured in a subsequent listing 16.2.4.8. These topical steroids were not included in this count. This reviewer also did not consider changes in antithrombotics (e.g. coumadin and its derivatives, heparin) or antiplatelet drugs (e.g. ticlopidine) as a reflection of worsening disease but rather as responses to changing INR.

Based on this analysis, there were 165/233 subjects (70.8%) of those in the UT-15 group and 163/266 (69.1%) of the vehicle group who did not receive new medications and did not have baseline medications increased in doses (these patients could have medications changed i.e. decreased but were not counted). There did not appear to be an overwhelming signal that subject's status was sufficiently altered to require less concurrent medications.

Concomitant medications by class of drug, at the end of study and at screening are shown in table below (derived from sponsor's Table 11.2.2.12 and 11.4.5). There were slight increases in the number of subjects treated with each category of drug for both treatments. There were far more subjects treated with anticoagulants at the end of the study than at baseline-screening. Other classes of drugs were only slightly increased over baseline. There were more subjects on vehicle versus UT-15 subjects taking diuretics at the end of the study relative to baseline (28 versus 20), calcium channel blockers (4 versus 3), other vasodilators (0 versus 6) and digoxin (11 versus 9).

Table 77. Medication changes (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Anticoagulants	Baseline	58 (52)	61 (54)	88 (82)	88 (73)	160 (68)	149 (64)
	Treatment	94 (85)	95 (84)	116 (92)	104 (87)	210 (89)	199 (85)
Calcium channel blockers	Baseline	50 (45)	49 (43)	48 (38)	48 (40)	98 (42)	97 (42)
	Treatment	52 (49)	50 (44)	49 (39)	51 (43)	101 (43)	101 (43)
Other vasodilators	Baseline	19 (17)	18 (16)	16 (13)	15 913)	35 (15	33 (14)
	Treatment	24 (22)	18 (16)	17 (14)	15 (13)	41 (17)	33 (14
Digoxin	Baseline	30 (27)	34 (30)	29 (23)	22 (18)	59 (25)	56 (24)
	Treatment	35 (32)	41 (36)	33 (26)	26 (22)	68 (29)	67 (29)
Diuretics	Baseline	54 (49)	69 (61)	75 (60)	57 (56)	129 (55)	136 (58)
	Treatment	71 (64)	82 (73)	86 (68)	74 (62)	157 (66)	156 (67)

Change in NYHA classification

This parameter was not measured after baseline. No change in subject NYHA status was available.

Dose response

There was no formal dose-response data available. Since subjects were forced titrated based on symptom improvement as well as tolerance to drug, any dose-related data is confounded by duration of time in the study. Dose response data could theoretically be defined by the walking effect at a given infusion rate of drug.

The relationship of infusion rate and walking distance at week 12 is shown in Figure 16. Both vehicle (P) and UT-15 (A) have positive non-zero slope effects. The intercepts of the two drugs differ. The intercept for vehicle is negative and significantly different from baseline.

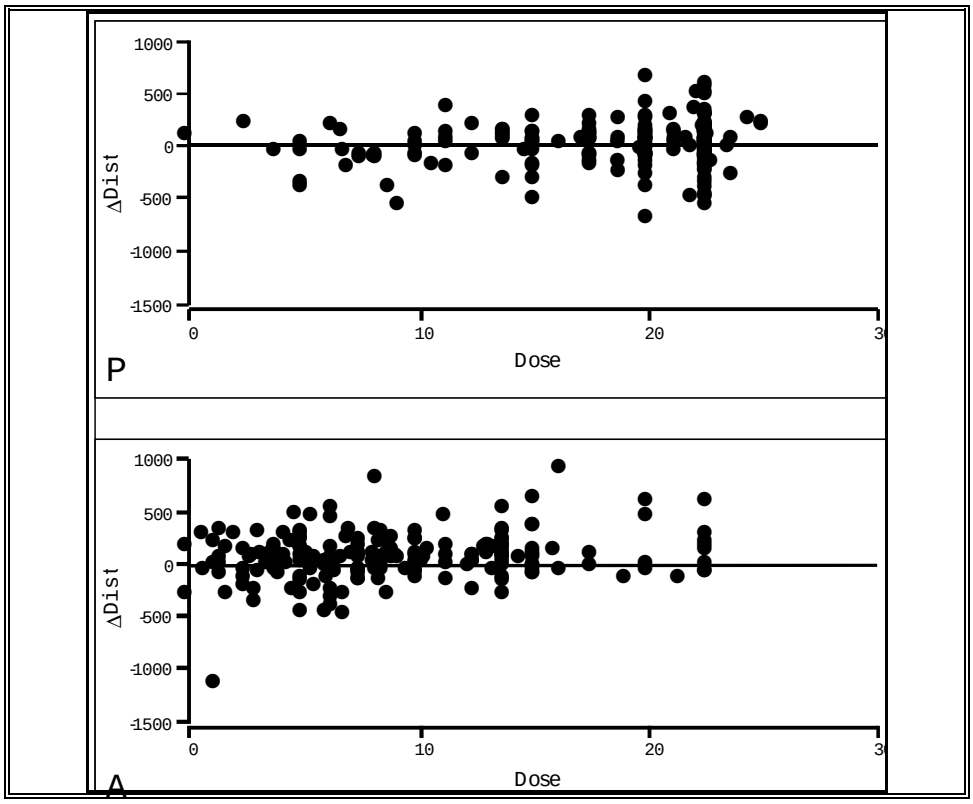


Figure 16. Change from baseline in walking distance (feet) by dose (studies P01:04, P01:05).
P=Vehicle; A=active treatment. Data derived from datasets for both studies combined, tables RANDCODE, WALK, and ODRUG. Horizontal line marks no change from baseline.

The data from the figure above were fitted to a straight line (linear least squares procedure) using JMP. The resulting fitted parameters and their confidence limits are shown in Table 78.

Table 78. Fit of change in walking distance (feet) by dose to y=m*DOSE+b.

	m±SD	P(m≠0)	b±SD	P(b≠0)
Vehicle	5.5±2.7	0.04	-106±52	0.04
UT-15	8.5±2.9	0.003	-28±30	0.4

Subgroup analysis based on baseline status

Dr. Lawrence, the FDA statistician analyzed the time-dependent effect of the various cohorts that were enrolled in this study .A linear mixed-effect model was used here as an exploratory analysis in order to see the treatment effect over time. This model assumes that those subjects who discontinued early, regardless of the reason for discontinuation, would have walking distances similar to those subjects who completed the study. Missing data can be predicted based on the performance of other subjects that have similar characteristics to the one with missing data.

Since each subject would theoretically have three measurements post-baseline, Dr Lawrence modeled the change from baseline as a quadratic function of time. The specific linear model that was used contained fixed-effects for treatment group, baseline distance walked, etiology, vasodilator use among secondary PH subjects, and time as a quadratic function. In addition, all two-way interactions between treatment group and the other variables as well as the two-way interactions between stratification (etiology/

vasodilator use) and time were included in the model. There were random effects for the intercept, slope, and the quadratic term for time. The strategy was to specify a complex model and let the data decide which terms were important. The curves for each stratification level at the average baseline walking distance are shown in Figure 13 on page 119.

From Figure 13, it appears that at Week 1, subjects in all strata in the vehicle group improved walking distance by an average of about 10 meters. Over the course of the trial, there was a gradual deterioration in the performance of all subjects, independent of origin. In the UT-15 group, the change at Week 1 was about 15 m in the SPH (no vasodilator) subgroup and about 20 m in the other two subgroups, but over the course of the trial, the improvement was maintained or increased slightly.

Kinetics

Pharmacokinetic measurements were collected on Days 2, week 1, week 6 and week 12. The kinetic data was not attached to this study report but was submitted separately as a biopharmaceutical report.

Tolerance

There is no information submitted that any effect of UT-15 lasts more than the 12-week duration of this study. No randomized withdrawal information of the study was performed to convincingly demonstrate a persistent drug effect. The concern that there may be tolerance arises from the large increase in dose of UT-15 in going from week 1 to week 6 or week 12 and the minimal change in walking distances over these dose increases. The doses are graphically displayed in Figure 12 on page 90. There were a greater than 4-fold increase in dose in going from the end of week1 1.2 ng/kg/min to week 6 (5.9 ng/kg/min). There was minimal change, however, in walking distance during the same period of time.

There does not appear to be adequate information available from pre-clinical, animal and biopharm data to rule out a potential of diminishing effect of long duration of UT-15 treatment. Mechanism of tolerance may include

- A decrease in the availability after long duration of infusion i.e. fibrosis at the infusion site may limit availability. Because infusion sites were rotated frequently, this is not likely.
- Metabolites may be produced that act in a counter-regulatory manner to the effect of UT-15 (the metabolic profile as well as the half-life of the known metabolites as well as the potential for the existence of uncharacterized metabolites remain a possibility.
- Down regulation of receptors or de-linking of receptors from regulatory proteins may have occurred.

A.4.4.8 Safety

A.4.4.8.1 Exposure

There were a total of 469 subjects who were randomized and received at least one dose of drug/vehicle. The mean (±SD) duration of exposure for those treated with UT-15 was 81.06 ± 17.1 days and for vehicle it was 82.83 ± 14.1 Days. There were 31 UT-15 and 16 vehicle subjects who were treated for less than 72 days (the lower limit of the window for the 12-week visit). Subjects were exposed to UT-15 for a total of 18,887 subject x days (51.75 subject x years) and to vehicle for 19,547 subject x days (53.55 subject x years). Exposure to vehicle was therefore 3.5% greater than that of UT-15 The mean dose of UT-15/vehicle are shown in Figure 12 on page 103.

The distribution of infusion rates for UT-15 and vehicle subjects are shown in Table 79. Approximately 50% of those treated with vehicle received doses of >20 ng/kg/min. For the UT-15 treated subjects the median dose was 9.3 ng/kg/min.

Table 79. Distribution of doses by week (P01:04-05)

Dose µg/kgmin	Week 1		Week 4		Week 8		Week 12	
	Veh N=231	UT-15 N=233	Veh N=228	UT-15 N=227	Veh N=221	UT-15 N=209	Veh N=217	UT-15 N=202
0 to 2.5	244	233	12	58	0	21	0	16
2.5 to 5.0	6	—	56	100	9	51	6	37
5.0 to 10	1	—	160	69	26	81	14	75
10 to 20	—	—	—	—	186	56	88	64
>20	—	—	—	—	—	—	109	10

More vehicle subjects were titrated upward and more UT-15 subjects were down titrated during the course of the study (Table 80). It should be noted that when doses were decreased, the usual reason was for either infusion site pain/reaction. There was no fixed dose decrease that was to occur in response to infusion site pain supervened. Trivial dose changes were often implemented as a consequence of infusion site pain. The reasons for dose decreases are shown in Table 81.

Table 80. Increases and decreases in dose (P01:04-05)[102]

	One or more increase		One or more decrease	
	Vehicle	UT-15	Vehicle	UT-15
Week 1-4	230	224	15	58
Week 5-8	226	203	19	70
Week 9-12	212	173	8	35

Table 81. Reasons for dose decreases (P01:04-05)

	Veh	UT-15		Veh	UT-15
Infusion site pain	1 (<1)	64 (27)	Headache	1 (<1)	9 (4)
Infusion site reaction	0 (0)	31 (13)	Vasodilation	0 (0)	9 (4)
Nausea	1 (<1)	11 (13)	Diarrhea	0 (0)	6 (3)
Pain	0 (0)	9 (4)	Vomiting	1 (<1)	6 (3)

Of the treated subjects who had dose reduction, 57 of the 64 UT-15 subjects with infusion site pain and 26 of the 31 subjects with infusion site reaction. For UT-15 infusion site pain and infusion site reaction were first noted at doses of 0- <2.5 ng/kg/min. Only six subjects had the onset of pain and 4 subjects with infusion site reaction had the onset of symptoms at doses > 2.5 ng/kg/min.

Approximately 65% of those treated with UT-15 complained of infusion site pain by the end of the first week of treatment. The percentage increased to approximately 90% complained of pain by the end of week 3. Nearly all subjects had infusion site pain by the end of week 12.

The fraction of subjects treated with opiates by the end of week 1 was 4%. This fraction increased to approximately 12% by the end of week 3 and 28% by the end of the study. The fraction of subjects treated with anti-inflammatory drugs was 16% at the end of week 1and increased to 28% at the end of week 3 and 44 % by the end of the 12-week

[102] *Sponsor's Table 12.1.2A*

study. The fraction of UT-15 who received either opiates opr anti-inflammatory drugs was 16% by the end of week 1, 32% by the end of week 3 and 52% by the end of the study.

It is, however, unclear whether the need for pain medication was continuous and therefore a necessary component of treatment or the pain medication as taken only on a PRN basis and therefore only an intermittent nuisance. Based on discussions with the sponsor, patients were offered a prescription and compliance and use of the pain medication was not further followed.

A.4.4.8.2 Deaths

There were a total of 19 deaths in or around the study. Nine of these deaths in people randomized to UT-15 and ten to vehicle. Subjects who died were: # 04/4017; #05/4503; #04/9006; #04/10002; #04/23002; #05/51007; #05/54005; #05/55005; and #05/58001 in the UT-15 group and 04/9012; #04/10001; #04/15003; #04/16003; #04/16006; #05/52006; #05/60006; #05/60015; #05/65004; #05/65011 in the vehicle group. The underlined subjects discontinued for reasons other than death but died during the 12-week window of the study. Capsular summaries are available in Table 82 below which contains the list of all subjects hospitalized.

A.4.4.8.3 Dropouts/discontinuations

There were 20 dropouts for adverse events or withdrawal of consent in the UT-15 group. One additional subject #4503 was listed as a dropout but died of sepsis.

A.4.4.8.4 Hospitalizations or prolongation of hospitalization:

There were 38 and 40 subjects, randomized to UT-15 and vehicle, respectively who were either hospitalized or whose hospitalization was prolonged. Two vehicle subjects were inadvertently administered UT-15 and were hospitalized after the cross-over while treated with active drug. Capsular summaries for those that were hospitalized, deteriorated or died are shown in Table 82.

Table 82. Capsular summaries for those who died, were hospitalized or whose hospitalization was prolonged (P01:04-05)

Study/ Subject[103] Arm Event	Description
√04/2019 UT-15	This was a 37- year old Caucasian female with pulmonary hypertension and SLE and NYHA Class III status. She was hospitalized for an allergic reaction to Bactrim, prescribed for a UTI.
04/2022 UT-15	This was a 35-year old Caucasian Female with pulmonary hypertension and systemic sclerosis and NYHA class III. Concomitant medications included furosemide, isradipine, oxygen and warfarin. She was hospitalized for guaiac positive stools.
04/3009 UT-15	This was a 38-year old Caucasian female subject with pulmonary hypertension and SLE and NYHA Class III status. The subject was hospitalized for pneumococcal meningitis.
04/4017 UT-15 death	This was a 32-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. She was hospitalized on day 21 of the study for worsened heart failure and eventually died.
05/4503 UT-15 ADR Pt died	This was a 36-year old Hispanic female with primary pulmonary hypertension and NYHA Class III status. The subject became septic status post a medical termination of pregnancy. The subject treated with antibiotics but subsequently died.
04/5003 UT-15	This was a 71-year old Caucasian female with pulmonary hypertension and limited scleroderma and NYHA Class IV. Concomitant medications included digoxin, enalapril and warfarin. She was hospitalized for diarrhea, rectal bleeding and vomiting. Warfarin was withheld and the subject was rehydrated.
04/5009 UT-15 ADR	This was a 51-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. She was hospitalized on day 2 (one-day post-catheterization) for a right groin hematoma and a collection of blood in the pelvis. The subject was not taking anticoagulants at the time of the event.
04/7004 UT-15 ADR	This was a 44-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt. She was NYHA Class II. The subject was hospitalized twice, once for hemoptysis and a possible upper lobe infiltrate (on day 35) once again for hemoptysis (on day 43). Endobronchial embolization was performed. Concomitant medications included digoxin and furosemide. Coumadin was stopped on the day of the first event.
04/9001 UT-15	This was a 30-year old Caucasian female with pulmonary hypertension and mixed connective tissue disease and NYHA Class III who was admitted to the hospital for nausea, vomiting dehydration and hyponatremia (serum sodium 126). The subject was given iv fluids and recovered.
04/9002 UT-15	This was a 61-year old Caucasian female with pulmonary hypertension and mixed connective tissue disease who was admitted because of diarrhea, pancytopenia (Hemoglobin = 8.9 g/dL; platelets 44 x 10^3/uL; WBC = 3,74 x 10^3/uL) and hyponatremia (Na+ = 117 mEq/L). She had recently been treated with cyclophosphamide. She was treated with fluid restrictions, electrolytes, dobutamine, prednisone and platelet and RBC transfusions. She recovered.
04/9006 UT-15 death	This was a 29-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt (atrial septal defect) and NYHA Class III status. She developed lightheadedness and bilateral loss of vision on day 2. A paradoxical embolism was suspected. The study drug was stopped. The next day the drug was commenced, New symptoms (facial droop and dysarthria) were noted. Angiography and thrombolysis were undertaken and a bird's nest filter placed to intercept any emboli from the lower limbs. The subject subsequently suffered seizures, with increased intracranial pressure. The subject deteriorated to brain death and subsequently expired.
04/9017	This was a 53-year old Caucasian female subject with primary pulmonary hypertension NYHA Class III. The subject was hospitalized for an acute psychiatric disturbance.

[103] √ *indicates non-fatal events the reviewer assess as cardiovascular in nature.*

Study/ Subject[103] Arm Event	Description
04/10002 UT-15 death	This was a 40-year old Caucasian female with pulmonary hypertension associated with mixed connective tissue disease and NYHA Class IV status. The subject was hospitalized on study day 57 with worsening right heart failure. Her condition deteriorated and she suffered an arrhythmia and died.
√04/10006 UT-15	This was a 46 year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 22 for altered renal function (BUN was 99 increasing to 115, Creatinine was 1.7 and increased to 2.5 mg/dL). The subject was hydrated with correction of the BUN (to 85mg/dL). The subject was again hospitalized on days 38 and again on day 57 for fluid overload.
√04/12002 UT-15	This was a 71 year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III status. The subject sustained a CVA on day 52 of treatment but continued on therapy.
04/12007 UT-15	This was a 70-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 86 for a pneumothorax post 12-week catheterization.
04/13001 UT-15	This was a 58-year Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject administered an excess of UT-15 (a bolus of 1.5 mL or approximately 1500 ng). The subject had severe pain at the infusion site and removed the subcutaneous catheter. The symptoms, upon arriving at the emergency room, consisted of vomiting, headache, neck ache and leg pain. The study drug was restarted.
√04/14005 UT-15	This was a 40-year old Caucasian female with a history of pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. After the 12-week catheterization the subject developed increasing dyspnea, chest pain and left shoulder pain and was hypoxemic. She was treated with supplemental oxygen improved over the next two days and was discharged.
√04/14009 UT-15	This was a 36-year old Hispanic female with pulmonary hypertension associated with a congenital systemic to pulmonary shunt. She was treated with digoxin, oxygen and warfarin. After heavy menstrual bleeding she was seen in the ER on day 69 with a complaint of lightheadedness and dyspnea. Her hemoglobin was 7.3 g/dL, the INR was 1.43. She was again hospitalized on day 79 with a diagnosis of acute right heart failure. She received transfusions as well as oxygen and diuretics.
05/14501 UT-15	This was a 41-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 48 an episode of acute hemolytic anemia.
√05/21501 UT-15	This was a 36-year old Hispanic female subject with primary pulmonary hypertension an NYHA Class III. The subject was hospitalized because she was hypoxemic associated with an acute flu syndrome. She recovered.
04/23002 UT-15 death	This was a 15-year old Native American female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class II status. The subject was found comatose, pulseless and hardly breathing. Attempted resuscitation was unsuccessful and the subject died.
05/24505 UT-15	This was a 49-year old Caucasian female with pulmonary hypertension as a consequence of a congenital systemic to pulmonary shunt. She was NYHA Class III. She was hospitalized on day 55 for dehydration.
05/50015 UT-15	This was a 52 year old Caucasian female with pulmonary hypertension and limited scleroderma and NYHA Class IV. The subject had a syncopal episode at cardiac catheterization on day 85 of the study. The event was attributed to a vasovagal event.
√05/50023 UT-15	This was a 37-year old Caucasian female with a history of pulmonary hypertension associated with mixed connective tissue disease and NYHA Class IV status. The subject had her hospitalization duration increased because of supraventricular tachycardia. On day 3 of treatment. The subject was again hospitalized on day 70 and 76 for worsening heart failure and pain at the infusion site.
05/51007 UT-15 death	This was a 28-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III status. The subject had a syncopal episode at the time of catheterization for week 12. The subject had an episode of bradycardia with loss of

Study/ Subject[103] Arm Event	Description
	consciousness. Intravenous atropine was administered. The subject developed A-V block and subsequently developed electromechanical dissociation and died. Autopsy revealed severe pulmonary hypertension with cor pulmonale. Inflammatory changes were noted in the myocardium.
√05/52001 UT-15	This was a 40-year old Caucasian male with primary pulmonary hypertension and NYHA Class III. The subject developed a recurrent event of atrial flutter and was treated with amiodarone.
05/53001 UT-15	This was a 48-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. The subject complained of asthenia. The asthenia was attributed to malfunction of the infusion pump. The subject was admitted to the hospital for pump repair on day 17 and again on 26.
05/53020 UT-15	This was a 61-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was taking acenocoumarol and furosemide. The subject developed an episode of melena. The INR at the time was 4.0. The hemoglobin was 4.9 g/dL. The subject received three units of packed red blood cells. At gastroscopy an active area of hemorrhagic gastritis was noted.
√05/53022 UT-15 deteriorate	This was a 42-year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 28 for worsening heart failure. Because of intolerable site pain in conjunction with the worsening of heart failure the subject was started on iv flolan.
√05/54005 UT-15 deteriorate	This was a 20-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital on day 43 for worsening hypoxemia and unstable hemodynamics. The subject was suspected of having had a pulmonary embolism (the subject was not on any anticoagulant at the time of enrollment because of a history of menorrhagia). No ventilation-perfusion scan was performed. The subject had two cardio-respiratory arrests and died.
√05/54014 UT-15	This was a 44 -year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt. The subject was admitted to the hospital with asthenia and increasing dyspnea. The subject was diagnosed with adrenal insufficiency and was treated with intravenous then oral hydrocortisone.
05/55005 UT-15 death	This was a 32-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class IV. The subject had an episode of syncope and hypotension associated with chest pain. The subject was treated with pressors. There was no statement re EKG changes or cardiac enzymes. The subject developed VF and died.
√05/58001 UT-15 deteriorate	This was a 39-year old Caucasian male with primary pulmonary hypertension and NYHA class III status. The subject was treated with spironolactone and warfarin. The subject was admitted to the hospital because of hemoptysis and weakness. The INR at admission was 6.09. The subject's status deteriorated. The subject developed metabolic acidosis and his renal function deteriorated. Ventilation worsened. The subject improved slightly then deteriorated and died.
√05/58006 UT-15 deteriorate	This was a 53-year old Caucasian subject with primary pulmonary hypertension and NYHA Class III status. The subject suffered a syncopal episode with chest pain. The subject was hospitalized on day 17, 28 and 38 of treatment. The subject, however, was subsequently started on intravenous flolan.
05/59003 UT-15	This was a 48 year old Caucasian female with primary pulmonary hypertension and NYHA Class II status. The subject was taking concurrent digoxin, furosemide and warfarin. The subject was hospitalized on day 81 with melena and marked asthenia. Warfarin was withheld for one day when the INR was subsequently measured as 1.14. Endoscopy revealed features of acute petechial gastritis.
√05/60005 UT-15 withdrew consent	This was a 43 year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 28 for purpura associated with a low platelet count 68,000 x 10^3. The subject also developed hemolytic anemia (Hemoglobin dropped from 13.9 to 9.6 g/dL) associated with an elevated

Study/ Subject[103] Arm Event	Description
	reticulocyte count (29%) and bilirubin (2.2 ng/dL). This subject also became profoundly hypoxemic and was treated with O_2. The subject withdrew consent from the study.
√05/65006 UT-15 Withdrew consent	This was a 48-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital on day 20 for bleeding at the infusion site. The subject was again hospitalized on day 64 for worsening pulmonary hypertension. Intravenous flolan was started.
√04/4001 Vehicle	This was a 33-year old Caucasian female with primary pulmonary hypertension and NYHA Class II. Shortly after the completion of the catheterization, when pressure was applied to the vascular access, she developed bradycardia (heart rate 27-30) that responded to atropine.
04/4009 Vehicle	This was a 34-year old female with pulmonary hypertension and systemic sclerosis and NYHA Class III status who was hospitalized for bronchitis. She was treated with vancomycin, Zosyn and azithromycin.
√05/7502 Vehicle	This was a 37-year old black female with pulmonary hypertension and SLE and NYHA Class III status. The subject was treated with hydrochlorothiazide and prednisone. She halted warfarin in anticipation of cardiac catheterization. The subject was hospitalized with pleuritic chest pain that was eventually diagnosed as a pulmonary embolism. A doppler ultrasound eventually showed a non-occlusive thrombus in popliteal and common femoral veins. She was discharged on warfarin and enoxaparin.
√04/8006 Vehicle deteriorate	This was a 50-year old Caucasian female with primary pulmonary hypertension and NYHA Class III. She was hospitalized on day 59 for increasing dyspnea, ascites and peripheral edema. She was discontinued from the study and iv flolan commenced.
√04/9012 Vehicle death	This was a 56-year old Caucasian male with primary pulmonary hypertension and NYHA ClassIV heart failure. The subject was admitted to the hospital on day 8 for worsening heart failure. The subject received inotropic support but deteriorated and died the same day.
04/9018 Vehicle	This was a 31-year old female Caucasian female subject with pulmonary hypertension associated with a congenital systemic to pulmonary shunt who suffered a right pneumothorax post catheterization.
04/10001 Vehicle death	This was a 65-year old male with pulmonary hypertension associated with a mixed connective tissue disease/CREST syndrome and NYHA Class IV. The subject was admitted to the hospital with acute respiratory distress after hematemesis. He was thought to have esophagitis and possible aspiration pneumonia. The subject was managed with mechanical ventilation and required vasopressors. The subject died 6 days later.
√04/12003 Vehicle	This was a 76-year old Caucasian female with primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 87 for chest pain. Angioplasty and stenting of the circumflex artery was performed.
√04/14001 Vehicle	This was a 35-year old Asian female with pulmonary hypertension associated with mixed connective tissue disease with NYHA class III status. She was admitted to the hospital in right heart failure on day 12 of treatment. She required dobutamine and furosemide. She was discharged five day later. She was again hospitalized on day 74 for a syncopal episode. The subject had a history of syncope. At the end of the study she was started on flolan.
04/15003 Vehicle death	This was a 23-year old Caucasian female with pulmonary hypertension and SLE/mixed connective tissue disease and NYHA Class II status. The subject was hospitalized for increasing dyspnea on day 25 of treatment. A transthoracic ECHO demonstrated a large pericardial effusion with possible tamponade. A pericardiocentisis was performed with removal of 1200 cc of fluid. The subject arrested and died.
04/16003 Vehicle death	This was a 67-year old Caucasian female with pulmonary hypertension associated with limited scleroderma and NYHA Class III heart failure. The subject was hospitalized on day 48 due to dyspnea and cough. The subject was again hospitalized on day 85 for acute respiratory distress. The subject was intubated but subsequently vomited with aspiration. The subject became febrile. The subject died 4 days later.
04/16006	The subject was a 57-year old Caucasian female with a history of primary pulmonary

Study/ Subject[103] Arm Event	Description
Vehicle Completed death	hypertension and NYHA Class III status. The subject developed ankle edema and acute dyspnea and was hospitalized on day 62. The subject was catheterized on day 75 of the protocol for the end of study hemodyanmics. The subject became hyposaturated, arrested and died 10 days later.
04/17006 Vehicle	This was a 60-year old Caucasian female with pulmonary hypertension associated with limited scleroderma , CREST syndrome and NYHA Class III status. The subject was hospitalized for pyrexia. All cultures were negative and the subject was discharged three days later. The subject subsequently developed hip pain. She was again hospitalized on day 14 of treatment for pyrexia. The pyrexia resolved three days later.
04/20006 Vehicle	This was a 36-year old Hispanic female with primary pulmonary hypertension and NYHA Class II status. She was treated with Acenocoumarol, chlorthalidone and oxygen. She was fatigued and had palpitations and experienced prolonged menorrhagia. Her hemoglobin on admission was 9.2 g/dL. She received two units of packed red blood cells with a rise in hemoglobin to 12.1 /dL and she was discharged.
√04/20007 Vehicle	This was a 42-year old Hispanic female subject with primary pulmonary hypertension and NYHA Class IV status. She developed worsening dyspnea and edema. She was admitted to the hospital where she was treated with diuretics, low dose dopamine and oxygen.
04/20010 Vehicle	This was a 19-year old Hispanic female with pulmonary hypertension and a systemic right to left shunt and NYHA Class III. On day 2, one-day post catheterization in which contrast was administered to confirm the presence of the PDA, her creatinine increased to 3.4 mg/dL. Baseline creatinine was 1.02 mg/dL. She was treated with hydration and her status improved after three days. Her creatinine was 1.4 mg/dL.
√04/22007 Vehicle	This was a 35-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized for dyspnea, cough, chest pain and abdominal bloating. A chest X-ray showed a right pleural effusion. The subject improved with intravenous diuretics.
05/22501 Vehicle	. This was a 63-year old Caucasian female with a history of pulmonary hypertension and systemic sclerosis and NYHA Class III status. She was admitted to the hospital on day 50 of treatment with increasing dyspnea. A focal infiltrate was observed on X-ray, possibly indicative of pneumonia. High resolution CT scan of the chest showed a right-sided pleural effusion and a small left-sided pleural effusion. She received oxygen and antibiotic. The subject was discharged from the hospital after 4 days.
05/22504 Vehicle died study P01:06	This was a 19-year old Caucasian female with primary pulmonary hypertension and NYHA Class II status. The subject was hospitalized at day 50 for worsening shortness of breath. The subject completed the study The subject was subsequently started on open-label UT-15 in Study P01:06 and did not improve. She was treated with iv flolan but died four days later.
√05/50003 Vehicle	This was a 35-year old Caucasian female with a history of primary pulmonary hypertension who was hospitalized on day 52 of treatment because of increased dyspnea and weight gain. She received increased diuretics, oxygen and diuretics.
√05/50014 Vehicle	This was a 50-year old Caucasian male with primary pulmonary hypertension and NYHA Class IV. The subject was hospitalized several times (on day 17, 35, 54 and 75) due to worsening heart failure. The subject required a dobutamine drip on day 81 of the study. The subject completed the study and was entered in Study P01:06. He died of a low cardiac output state two weeks later.
√05/50022 Vehicle	This was a 21-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. The subject The subject was hospitalized due to worsening edema and hyponatremia on day 56 of treatment. The subject was discharged after three days. The subject was again hospitalized on day 72 for increasing edema and weight gain, She was discharged after 4 days.
05/52003 Vehicle	This was a 30-year old Caucasian female with pulmonary hypertension with a congenital systemic to pulmonary shunt and NYHA Class III. The subject was hospitalized on day 53 for diarrhea and vomiting. This subject was inadvertently administered UT-15.which was suspected since the infusion site was red and swollen.

Study/ Subject[103] Arm Event	Description
05/52004 Vehicle	This was a 27-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III. The subject was taking bumetanide, diltiazem, phenprocoumon and sprionolactone at the time of the event. The subject was hospitalized on day 32 and 47. The subject developed epistaxis and anemia. The subject was hospitalized a second time for infusion site pain. The subject at some point had inadvertently been switched to UT-15.
05/52006 Vehicle ADR Died	This was a 49-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject developed cold and fever (39° C). She became dyspneic and weak and required assisted ventilation and pressor support. She subsequently developed lactic acidosis, acute renal failure, ischemic hepatitis and finally cardiogenic shock and died.
05/53014 Vehicle	This was a 61-year old Caucasian male with pulmonary hypertension and systemic sclerosis with NYHA Class III status. The subject was hospitalized on day 67 for gout. Concomitant medications included digoxin, fuosemide, isosorbide mononitrate, phenprocoumon and verapamil.
05/54007 Vehicle	This was a 37-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject had a syncopal episode with passage of stool. The subject was discharged two days later.
05/54027 Vehicle	This was a 62-year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 49 for edema and right heart failure. The subject was treated with intravenous furosemide.
√05/54028 Vehicle deteriorate	This was a 27-year old Caucasian female and primary pulmonary hypertension and NYHA Class III status. Her status deteriorated to NYHA Class IV. She was treated with oxygen and pressors. She was discharged on intravenous flolan.
√05/56003 Vehicle	This was a 66-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 47 of treatment because of worsening heart failure. The dose of diltiazem was adjusted and the subject improved and was discharged.
05/60006 Vehicle death	This was a 17-year old Caucasian female with primary pulmonary hypertension and NYHA Class IV status. Concomitant medications included heparin and nifedipine. The subject was hospitalized on treatment day 27 for hemoptysis. The subject was hospitalized again on day 60 of treatment for worsening dyspnea. The subject arrested and died.
05/60013 Vehicle	This was a 52- year old male with primary pulmonary hypertension and NYHA Class II. The subject was hospitalized on day 51 with pneumonia and hemoptysis. X-rays showed lung consolidation. A white blood cell count was 17,000. The subject was discharged after 19 days.
05/60015 Vehicle death	This was a 19 year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject and marked worsening of status and was admitted to the hospital on day 47. The subject's status worsened and the subject died the following day.
√05/64003 Vehicle deteriorate	This was a 41 year old Caucasian male with pulmonary hypertension and a congenital systemic to pulmonary shunt NYHA Class III status The subject was admitted on day 18 because of hemoptysis. The investigator decided to unblind this subject. The subject was started on flolan. The subject was categorized as having deteriorated.
05/65001 Vehicle	This was a 25 year old Caucasian male with primary pulmonary hypertension and NYHA Class II status. The subject was hospitalized for a manic reaction on day 43 of treatment.
05/65004 Vehicle death	This subject was a 51-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 18 for worsening pulmonary hypertension. His status worsened and he died.
√05/65011 Vehicle deteriorate	This was a 59-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 65.for worsening pulmonary hypertension. The subject was started on flolan. The subject died approximately 2 weeks later.

Study/ Subject[103] Arm Event	Description
05/66005 Vehicle	This was a 34-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject awoke at night with a short episode of dyspnea that lasted approximately 45 minutes. The episode revolved. The subject was admitted to the hospital with a negative work up.
05/66008 Vehicle	This was a 47-year old Caucasian male with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital for the feeling of a swollen tongue and pruritis. An aphthous ulcer was present on the lower lip. The subject was treated with an antihistamine and discharged. The event was attributed to a possible viral syndrome.
05/66010 Vehicle deteriorate	This was a 72-year old Caucasian male with primary pulmonary hypertension and NYHA Class IV status. The subject sustained worsening of pulmonary hypertension. The subject was admitted to the hospital on day 45 of treatment. The subject was started on flolan and discontinued from the study.

A.4.4.8.5 Adverse events listed as severe

There were a total of 146 (61.9%) subjects on UT-15 and 47 (20.2%) subjects on vehicle who had adverse events labeled as severe. Table 83 contains those adverse events that were categorized as severe in at least two subjects in either treatment group.

Table 83. Severe adverse events with n≥2 in either group (P01:04-05)

Event	Veh	UT-15	Event	Veh	UT-15
Any	47 (20.2%)	146 (61.9%)			
Infusion site pain	4 (1.7%)	93 (39.4%)	Shock	1 (0.4%)	2 (0.9%)
Infusion site reaction	2 (0.9%)	90 (38.1%)	Overdose	0 (0%)	2 (0.8%)
Infusion site bleed/bruise	2 (0.9%)	10 (4.2%)	Insomnia	0 (0%)	2 (0.8%)
Rash	0 (0%)	10 (4.2%)	Hemolytic anemia	1 (0.4%)	2 (0.8%)
Headache	4 (1.7%)	8 (3.4%)	Diarrhea	0 (0%)	2 (0.8%)
Pain	2 (0.9%)	6 (2.5%)	Contact dermatitis	0 (0.8%)	2 (0.8%)
Heart failure	11 (4.7%)	6 (2.5%)	Epistaxis	0 (0%)	2 (0.8%)
Edema	0 (0%)	4 (1.7%)	Fever	2 (0.9%)	1 (0.4%)
Hypoxia	1 (0.4%)	4 (1.7%)	Chest pain	3 (1.3%)	1 (0.4%)
Pulmonary hypertension	4 (1.7%)	4 (1.7%)	Cough increased	3 (1.3%)	1 (0.4%)
Syncope	3 (1.3%)	4 (1.7%)	Dyspnea	5 (2.1)	1 (0.4%)
Vaodilatation	0 (0%)	4 (1.7%)	Anorexia	2 (0.9%)	1 (0.4%)
Nausea and vomiting	1 (0.4%)	3 (1.3%)	Asthenia	2 (0.9%)	1 (0.4%)
Vomiting	0 (0%)	2 (0.8%)	Hemoptysis	2 (0.8%)	0 (0%)
Anemia	1 (0.4%)	2 (0.8%)	Malaise	2 (0.8%)	0 (0%)

There were far more subjects with infusion site reaction in the UT-15 group whose intensity was labeled as severe. Severe symptoms of heart failure and dyspnea was more frequent in the vehicle group; edema and hypoxia was, however, more frequently in the UT-15 group

Other adverse events listed as severe in intensity in one subject in that treatment are listed below.

Adverse events labeled as severe in a single subject that occurred in the UT-15 group were

Abdominal pain; Ascites; Cellulitis; Drug level decreased; Injection site reaction; Injection site pain; Injection site reaction; Sepsis; Viral infection; Atrial flutter; Bradycardia; Embolus; Hypotension; Migraine; Supraventricular tachycardia;

vascular disorder; Hematemesis; Hemorrhagic gastritis; Melena; Nausea; Rectal Hemorrhage; Adrenal cortical insufficiency; Pancytopenia; Dehydration; Gout; Peripheral edema; Myalgia; Myasthenia; Abnormal gait; Acute brain syndrome; Anxiety; Cerebral hemorrhage; Cerebral infarct; Dizziness; Hemiplegia; Psychosis; Speech disorder; Thinking abnormal; Withdrawal syndrome; Sweating; Visual field defect; Pruritis and Dysuria.

Adverse events labeled as severe that occurred in one subject in the vehicle group were:

Flu syndrome; Viral infection; Bradycardia; Congestive heart failure; Heart arrest; Hypotension; Pericardial effusion; Esophagitis; Nausea; Coagulation time increased; Myeloma; Gout; Hyponatremia; Peripheral edema; Convulsion; Depression; Dizziness; Manic Reaction; Paresthesia; Respiratory Apnea; Pruritis; Cute kidney Failure and Kidney failure;

A.4.4.8.6 Overall adverse events[104]

Adverse events of any intensity were fairly frequent. 231/233 or (99.1 %) of those in the UT-15 group and 218/236 (92.3%) of those in the vehicle group. The most common system involved was skin and appendages, with 222/233 (95.2%) and 155/236 (65.8%) subjects in the UT-15 and vehicle groups, respectively, had adverse events listed. The difference in the event rate reflects the irritating effect of the active treatment.

There was an increase adverse event rate among UT-15 subjects for “body as a whole”, “digestive”, “metabolic”, “nutritional” and “nervous system”. The specific adverse events increased in the UT-15 versus vehicle groups were “jaw pain” (13% versus 5%); “diarrhea” (25% versus 15%), “anorexia” (5 % versus 2%); and “nausea and vomiting” (3% versus 0.9%). With respect to the “Nutritional and Metabolic system”, “edema” (9% versus 3%) was increased in the UT-15 group. With respect to “Nervous system”, “vasodilatation” was increased (11% versus 5%).

“Chest pain” (9% versus 4%), “dyspnea” (8% versus 3%), “cough” (8% versus 35); and “infusion site bleeding” (44 versus 34) was more frequent in the vehicle group than in the UT-15 group.

[104] *From sponsor’s Table 14.3.2.1.2A.*

Table 84. Adverse events (P01:04-05)[105]

	Veh N=236	UT-15 N=233		Veh N=236	UT-15 N=233
Any	218 (92%)	231 (98%)			
Body as a whole	131 (56%)	129 (55%)	Nervous	71 (30%)	51 (22%)
Headache	54 (23%)	64 (27%)	Vaodilatation	25 (11%)	11 (5%)
Jaw Pain	11 (5%)	31 (13%)	Dizziness	21 (9%)	19 (8%)
Pain	25 (11%)	28 (12%)	Insomnia	14 (6%)	8 (3%)
Infection	20 (9%)	21 (9%)	Anxiety	9 (4%)	11 (6%)
Flu syndrome	9 (4%)	11 (5%)			
Asthenia	7 (3%)	11 (5%)			
Chest pain	20 (9%)	10 (4 %)			
Abdominal pain	10 (4%)	8 (3%)			
Back pain	12 (5%)	6 (3%)			
Fever	11 (4%)	6 (3%)			
Cardiovascular	60 (26%)	46 (20%)	Respiratory	59 (25%)	79 (34%)
Hypotension	5 (2%)	9 (4%)	Pharyngitis	13 (5%)	21 (9%)
Heart failure	17 (7%)	7 (3%)	Epistaxis	10 (4%)	4 (2%)
Hemorrhage	13 (6%)	7 (3%)	Dyspnea	8 (3%)	19 (8%)
Syncope	12 (5%)	7 (3%)	Cough Increased	7 (3%)	19 (8%)
Digestive	74 (32%)	105 (45%)	Skin and Appendages	222 (94%)	155 (67%)
Diarrhea	36 (15%)	58 (25%)	Infusion site pain	200 (85%)	62 (27%)
Nausea	41 (18%)	52 (22%)	Infus site reaction	196 (83%)	62 (27%)
Vomiting	14 (6%)	12 (5%)	Infus site bleed/bruise	79 (34%)	102 (44%)
Anorexia	4 (2%)	11 (5%)	Rash	32 (14%)	26 (11%)
Nausea, vomiting	2 (1%)	7 (3%)	Pruritis	19 (8%)	14 (6%)
Melena	0 (0%)	5 (2%)			
Endocrine	2 (0.9%)	1(<1%)	Special Senses	3 (1%)	7 (3%)
Hematol, lymphatic	33 (14%)	19 (8%)	Urogenital	14 (6%)	11 (5%)
Ecchymosis	27 (12%)	9 (4%)			
Metabolic and	30 (13%)	47 (20%)			
Nutritional	6 (3%)	21 (9%)			
Edema	16 (7%)	11 (5%)			
Peripheral edema	0 (0%)	5 (2%)			
Hypokalemia					
Musculoskeletal	14 (6%)	10(4%)			

Relationship of dose to adverse events. There was no parallel dose group. No conclusions related to dose related events can definitively be made. Table 1.46 contains events occurring in greater than 10 subjects in any group as well s the dose at which onset of the event was noted. The percentages reflect the number of events divided by the number of subjects who received that dose.

Most adverse events, however, were evident at the lowest infusion rate (0-2.5 ng/kg/min). In particular, infusion site reaction and infusion site pain occurred in most subjects 72-75% of the UT-15 group at the lowest dose. The likelihood is that this origin with a low dose is a surrogate for early onset of events.

[105] *The sponsor treats those who inadvertently received UT-15 but were randomized to the Vehicle group as UT-15 patients. Clearly this is inaccurate. This reviewer, however did not modify the fractions.*

Table 85. Adverse events by dose (P01:04-05)[106]

		Dose level (ng/kg/min)						Total
		0	**0-2.5**	**2.5-5.0**	**5.0-10**	**10-20**	**>20**	
Receiving dose	UT-15	31	236	213	162	81	11	236
	Veh	12	233	228	219	199	111	233
Body as a whole								
Headache	UT-15	1 (3%)	35(15%)	11 (5%)	11 (7%)	2 (2%)	1 (9%)	61
	Veh	0	27 (12%)	10 (4%)	8 (4%)	6 (3%)	3 35)	54
Jaw Pain	UT-15	1 (3%)	15(6%)	7 (3%)	6 (4%)	1(15)	0	30
	Veh	0	4 (2%)	1 (<1%)	3(1%)	2 (1%)	1 (1%)	11
Pain	UT-15	2 (6%)	14 (6%)	6 (3%)	4 (2%)	2(2%)	0	28
	Veh	0	8 (3%)	6 (3%)	3 (1%)	7 (4%)	1 (1%)	25
Infection	UT-15	0	9 (4%)	5 (25)	4 (2%)	1(1%)	1 (9%)	20
	Veh	0	6 (3%)	7(3%)	5 (2%)	2 (1%)	0	20
Asthenia	UT-15	0	5 (2%)	4(2%)	1 (<1%)	1(1%)	0	11
	Veh	0	2 (1%)	1(<1%)	2 (1%)	2 (1%)	0	7
Flu Syndrome	UT-15	0	8 (3%)	1 (<1%)	0	2 (2%)	0	11
	Veh	0	0	2 (1%)	3 (1%)	4 (2%)	0	9
Chest Pain	UT-15	0	4 (2%)	4 (2%)	1 (<1%)	1 (1%)	0	10
	Veh	0	4(2%)	4 (2%)	3 (1%)	9 (5%)	0	20
Back pain	UT-15	0	4 (2%)	2 (1%)	0	0	0	6
	Veh	0	4(2%)	2 (1%)	3 (1%)	2 (1%)	0	11
Abdominal pain	UT-15	0	5 (2%)	2 (1%)	0	1 (1%)	0	8
	Veh	0	6 3%)	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)	10
Fever	UT-15	0	2 (1%)	1 (<1%)	2 (1%)	0	0	5
	Veh	0	3 (1%)	3 (1%)	0	4 (2%)	0	10
Cardiovascular								
Heart Failure	UT-15	0	3 (1%)	2 (1%)	2 (1%)	0	0	7
	Veh	0	2 (1%)	3(1%)	3 (1%)	8 (4%)	1(1%)	17
Hemorrhage	UT-15	0	4 (2%)	2 (1%)	0	1 (1%)	0	7
	Veh	0	4 (2%)	2 (1%)	6 (3%)	1 (1%)	0	13
Syncope	UT-15	0	2 (1%)	2 (1%)	1 (1%)	2 (2%)	0	7
	Veh	0	2 (1%)	4 (2%)	3 (1%)	3 (2%)	0	12
Digestive								
Diarrhea	UT-15	0	22 (9%)	22 (10%)	10 (6%)	3 (3%)	0	57
	Veh	0	17 (7%)	7 (3%)	8 (4%)	4 (2%)	0	36
Nausea	UT-15	0	25 (11%)	13 (6%)	8 (5%)	4 (4%)	0	50
	Veh	0	19 (8%)	8 (4%)	10 (5%)	4 (2%)	0	41
Vomiting	UT-15	1 (3%)	6 (3%)	3 (1%)	2 (1%)	0	0	12
	Veh	0	6 (3%)	4 (2%)	1 (<1%)	3 (2%)	0	14
Anorexia	UT-15	0	5 (2%)	2 (1%)	4 (2%)	0	0	11
	Veh	0	3 (1%)	0	1(<1%)	0	0	4
Hematologic and lymphatic								
Ecchymosis	UT-15	0	8 (3%)	1 (<1%)	0	0	0	9
	Veh	0	5 (2%)	12 (5%)	5 (2%)	2 (1%)	2 (2%)	26
Metabolic and nutritional								
Edema	UT-15	1 (3%)	9 (4%)	8 (4%)	2 (1%)	0	0	20
	Veh	0	3 (1%)	1 (<1%)	2 (1%)	0	0	6
Peripheral edema	UT-15	0	7 (3%)	3 (1%)	0	1 (1%)	0	11
	Veh	0	1(<1%)	8 (4%)	4 (2%)	3 (1%)	0	16
Nervous								
Dizziness	UT-15	0	12 (5%)	2 (1%)	5 (3%)	2 (2%)	0	21

[106]*Adverse events occurring in at least 10 subjects in either group and the dose at onset and percentage of those at the dose who had the event*

		Dose level (ng/kg/min)						Total
		0	0-2.5	2.5-5.0	5.0-10	10-20	>20	
	Veh	0	8 (3%)	3 (1%)	4 (2%)	4 (2%)	0	19
Vasodilation	UT-15	1 (3%)	15 (6%)	5 (2%)	3 (2%)	1 (1%)	0	25
	Veh	0	6 (3%)	4 (2%)	0	0	1 (1%)	11
Insomnia	UT-15	0	9 (4%)	4 (2%)	0	1 (1%)	0	14
	Veh	0	2 (1%)	2 (1%)	3 (1%)	1 (1%)	0	8
Respiratory								
Pharyngitis	UT-15	0	5 (2%)	4 (2%)	3 (2%)	0	0	12
	Veh	0	8 (3%)	4 (2%)	2 (1%)	6 (3%)	1(1%)	21
Epistaxis	UT-15	0	5 (2%)	3 (1%)	2 (1%)	0	0	10
	Veh	0	0	0	1 (<1%)	0	0	1
Cough increased	UT-15	1 (3%)	2 (1%)	3 (1%)	1 (1%)	0	0	4
	Veh	0	4 (2%)	4 (2%)	5 (2%)	4 (2%)	2 (2%)	19
Dyspnea	UT-15	1 (3%)	3 (1%)	3 (1%)	1 (1%)	0	0	8
	Veh	1 (8%)	4 (2%)	3 (1%)	8 (4%)	2 (1%)	1 (1%)	19
Skin and appendages								
Infusion site pain	UT-15	2 (6%)	171 (72%)	17 (8%)	7 (4%)	0	0	197
	Veh	0	27 (12%)	13 (6%)	17 (8%)	5 (2%)	0	62
Infusion site reaction	UT-15	0	176 (75%)	8 (4%)	5 (3%)	4 (4%)	0	193
	Veh	0	26 (11%)	15 (7%)	14 (6%)	6 (3%)	1(1%)	62
Infusion site bleed/bruise	UT-15	0	36 (15%)	19 (9%)	19 (12%)	5 (5%)	0	79
	Veh	0	35 (15%)	26 (11%)	26 (12%)	14 (7%)	1(1%)	102
Rash	UT-15	1 (3%)	24 (10%)	4 (2%)	2 (1%)	0	0	31
	Veh	0	13 (6%)	2 (1%)	4 (2%)	3 (2%)	2 (2%)	24
Pruritis	UT-15	0	10 (4%)	7 (3%)	1 (1%)	0	1 (9%)	19
	Veh	0	4 (2%)	2 (1%)	1 (<1%)	5 (3%)	1 (1%)	13

A.4.4.8.7 Overdose

The sponsor lists eight subjects who had an adverse event that was classified as either overdose or drug excess. The most common organs effected by drug excess were skin (infusion site pain, infusion site reaction), gastrointestinal (vomiting, diarrhea, nausea, abdominal cramps), musculoskeletal (neck and leg aches), and vasodilatation (headache, flushing and near syncope).

Subject #13001: Developed symptoms of headache, leg aches, neck aches and vomiting after inadvertently flushing of her tubing prior to changing tubing.

Subject #52003: Inadvertently was given UT-15 at a dose of 10 ng/kg/min. Subject had been on vehicle up to that time. The subject developed vomiting and diarrhea. The dose was decreased to 8.5 ng/kg/min and the symptoms resolved..

Subject #52004: Inadvertently was given UT-15 at a dose of 8.5 ng/kg/min. This subject had been on vehicle up to that time. The subject developed pain at the infusion site. The dose was decreased to 6.25 ng/kg/min and the symptoms resolved.

Subject #53011:This subject's adverse event was classified as "excess UT-15". The dose of UT-15 was 15 ng/kg/min. This, however, was the appropriate dose for this subject. The symptoms included headache, nausea, diarrhea and abdominal cramps. Symptoms resolved upon lowering the dose to 12.5 ng/kg/min.

Subject #3006: This subject received 11 ng/kg/min inadvertently. The dose should have been 5 ng/kg/min. Symptoms included nausea, diarrhea and flushing, with improvement of symptoms with decrease in dose.

Subject #53004: Listed as having drug overdose due to inadequate bolus delivery. No additional information was supplied with the summary.

Subject #19501: This subject flushed the line with a bolus of 50 µg. The symptoms were nausea, vomiting and near syncope.

Subject #2004: Inadvertently was crossed over to UT-15 at a dose of 15 ng/kg/min. Symptom included gastrointestinal upset, leg cramps and redness at the infusion site.

A.4.4.8.8 Discontinuations without down-titration

There is little data with respect to the consequence of abruptly terminating UT-15 therapy. Although there were 25 subjects who discontinued UT-15 therapy, fifteen were down titrated as per protocol. Of the other ten subjects, six were started on Flolan. Four of these subjects were immediately started on Flolan. The two subjects who discontinued UT-15 and were not immediately started on Flolan apparently had no sequelae to the discontinuation of UT-15. One of these subjects actually discontinued UT-15 twice, with the highest dose at the time of discontinuation of 5 ng/kg/min. No sequelae were noted either the first or second time the subject discontinued treatment.

There were four subjects who discontinued UT-15 therapy and did not start Flolan. For three of the subjects the dose at which discontinuation occurred was very low, 2.5 ng/kg/min (2 subjects), and 1.25 ng/kg (1 subject). No sequelae were noted. The fourth subject discontinued from a dose of 5.0 ng/kg/min with no sequelae.

In summary, there were few subjects who abruptly discontinued from significant doses of UT-15 without immediate flolan therapy. Among the few who did no sequelae were noted.

A.4.4.8.9 Hemolytic anemia/ pancytopenia

Two subjects treated with UT-15 had hemolytic anemia. These subjects #60005 and #14501 are described in Table 82. One subject discontinued treatment and the other remained in the study on a lower dose. One additional UT-15 subject had pancytopenia (pt #9002). This subject is also described in Table 82. This subject also continued on therapy. Given the rechallenge, the relationship to UT-15 is unclear.

A.4.4.8.10 Vital signs

Vital signs were routinely measured during the first dose (a really low dose) of UT-15 or vehicle. Over the first 8 hours there was a drop in systolic/diastolic blood pressures of 4.5/1.2-mmHg in the UT-15 group and a drop of 5.8/4.6-mm Hg in the vehicle group. Heart rates were decreased 1.2 BPM in the UT-15 group and decreased 1.2 BPM in the vehicle group, at the end of the 8-hour period. These results are not adequate to rule out hemodynamic changes with credible doses of UT-15.

A.4.4.8.11 Orthostatic effects

Despite the association of prostacyclin agonists with changes in hemodynamics vital signs were not collected when infusion rates were increased. No standing measurements were performed, so no orthostatic values were available.

A.4.4.8.12 Laboratory

Laboratory values were collected at baseline and week 12 or at termination if less than 12 weeks. A central laboratory assayed all laboratory specimens, with the exception of coagulation profiles, which were assayed at the local site. The following chemistry, hematology and other laboratories were measured:

Chemistry: sodium, potassium, chloride, bicarbonate, CO_2, calcium, albumin, BUN/urea, total bilirubin, LDH, ALT/SGPT, AST/SGOT, creatinine.

Hematology: RBC count, hemoglobin, hematocrit, plactelet cout, WBC count/differential.

Other labs: coagulation times, urinalysis, β-hCG pregnancy test.

Any abnormalities in the values of chemistry and hematology must be interpreted in the context of the large number of concurrent therapies used in the studied population. In particular, diuretics were frequently used in this population and abnormalities in electrolytes and other laboratory values are to be expected i.e. changes in BUN/creatinine. Anticoagulants were frequently administered and consequently bleeding with drops in hemoglobin and hematocrit would be anticipated. There was also an asymmetry in the use of anti-inflammatory drugs, which were more frequently administered to the UT-15 group that could potentially alter predispose to bleeding i.e. a decrease in hematocrit.

Chemistry

Serious adverse events associated with abnormalities in chemistry. There were several subjects who were hospitalized in association with serious events associated with changes in chemistries. Capsular summaries of these subjects follow:

UT-15

#04/9001 had hyponatremia in association with vomiting and diarrhea;

#04/9002 had hyponatremia associated with diarrhea;

#04/10006 had elevated BUN associated with worsened renal function

#05/58001 had metabolic acidosis associated with deteriorated renal function

#05/60005 had hyperbilirubinemia associated with hemolytic anemia

Vehicle

#04/20010- had elevated creatinine associated with dye-induced renal failure

#05/52006- had lactic acidosis associated with renal failure

#05/53014 was hospitalized for gout

#05/50022- was hospitalized for worsening edema and hyponatremia.

Chemistry associated adverse events of any severity. The chemistry events listed as an adverse event is shown in Table 86.

Table 86. Chemistry abnormalities considered adverse events (P01:04-05)

	Vehicle	UT-15		Vehicle	UT-15
Liver damage	1 #50019	0	Alkalosis	0	1 #15007
Adrenal cortical insufficiency	0	1 #54014	BUN increased	0	1 #03012
Hypokalemia	0	5 #10025 #15005 #50009 #10002 #52004	Electrolyte abnormality	0	1 #50009
Gout	1 #53014	3 #10022 # 58009 #17003	Creatinine increased	1 #0210	0
Hyperkalemia	0	3 #58001 #9001 #10002	Kidney failure abnormal	0	1 #10006
Hyponatremia	2 #50022 #50014	2 #9001 #9002	Acute kidney failure	1 #20010	0
SGOT increased	2 #23001 #19503	0	Kidney failure	1 #9012	0
Bilirubenemia	2 #50020 #60013	1 #60009			

There were five subjects with hypokalemia and three with hyperkalemia, all in the UT-15 treated subjects. The other laboratory adverse events were randomly scattered between the two treatments.

Baseline, week 12 data and change from baseline information are shown in Table 87. The ranges that are shown are expanded to cover the normal range for the whole study population and are expanded to include the age ranges (> 8-75 years) and both genders who enrolled into the study. The data below reflect the pooled studies.

Table 87. Chemistry findings (P01:04-05)

Parameter Norm range		Baseline		Week 12 change		
		Veh	UT-15	Veh	UT-15	P-value
Albumin 2.9-4.9 g/dL	N x±SE	223 4.0±0.03	225 3.9±0.03	203 -0.04±0.02	186 0.02±0.03	0.14
Alk phosphatase 31-385 U/L	N x±SE	220 91±3	223 97±4	202 3.7±1.6	178 0.0±2.9	0.186
Total bilirubin 0.2 –1.2 mg/dL	N x±SE	223 1.0±0.04	225 1.0±0.05	202 0.12 ±0.03	185 -0.10±0.03	<0.0001
SGPT 6-43 U/L	N x±SE	223 29±2	224 27±1	203 -2.6±1.2	185 -2.8±1.2	>0.5
SGOT 9-40 U/L	N x±SE	223 31±1	224 30±1	203 -1.1±0.9	185 -1.4±1.0	0.35
LDH 53-325 U/L	N x±SE	211 245±5	221 248±5	191 4.4±3.8	175 -22±4	<0.0001
BUN/Urea 4-24 mg/dL	N x±SE	224 16±1	225 17±1	206 1.2±0.3	187 -0.3±0.7	0.0003
Creatinine 0.3-1.3 mg/dL	N x±SE	224 0.9±0.02	225 0.9±0.02	206 0.01±0.01	187 -0.01±0.02	0.12
Sodium 132-147 mEq/L	N x±SE	224 140±0.3	223 140±0.2	206 -0.4±0.3	185 -0.3±0.3	>0.5
Potassium 3.4- 5.4 mEq/L	N x±SE	211 4.2±0.03	220 4.1±0.04	191 -0.05±0.04	175 -0.01±0.04	>0.5
Calcium 8.4-10.3 mg/dL	N x±SE	224 9.0±0.04	224 9.1±0.04	205 -0.01±0.04	186 -0.10±0.04	0.25
Chloride 94-112 mEq/L	N x±SE	224 104±0.3	223 103±0.3	206 -0.2±0.3	185 0.0±0.3	>0.5
Bicarbonate 17.0-30.6 mEq/L	N x±SE	221 22±0.2	225 23±0.2	201 0.5±0.2	186 0.1±0.2	0.16

There were decreases in group means in the UT-15 group relative to Vehicle for total bilirubin, LDH and BUN/urea. The sponsor attributes the change to a decrease in hepatic congestion.

Shift tables for those measurements that were altered are shown in Table 88.

Table 88. Selected chemistry shifts (P01:04-05)[107]

			Week 12					
			Low		Normal		High	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
LDH 53-325 U/L	Baseline	Low	0 (0%)	3 (2%)	8 (4%)	5 (3%)	3 (1%)	1(<%)
		Normal	6 (3%)	12 (6%)	157 (75%)	151 (77%)	14 (7%)	8 (4%)
		High	1 (<1%)	0 (0%)	9 (4%)	14 (7%)	11(5%)	2 (1%)
SGOT 9-40 U/L		Low	0 (0%)	0 (0%)	1 (<1%)	7 (4%)	0 (0%)	0 (0%)
		Normal	4 (2%)	3 (2%)	162 (78%)	149 (76%)	12 (6%)	12 (6%)
		High	1 (<1%)	1 (>1%)	11(5%)	14 (7%)	18 (9%)	10 (5%)
Total bilirubin 0.2 –1.2 mg/dL		Low	0 (0%)	0 (%)	1 (<1%)	6 (3%)	0 (0%)	0 (0%)
		Normal	5 (2%)	3 (2%)	140 (67%)	134 (68%)	19 (9%)	7 (4%)
		High	1 <1%)	2 (1%)	5 (2%)	16 (8%)	38 (18%)	28 (14%)
BUN/Urea 4-24 mg/dL		Low	0 (0%)	0 (0%)	0 (0%)	5 (3%)	0 (0%)	1 (<1%)
		Normal	3 (1%)	4 (2%)	172 (82%)	152 (77%)	17 (8%)	11 (6%)
		High	0(0%)	0 (0%)	5 (2%)	17 (9%)	12 (6%)	6 (3%)
Creatinine 0.3-1.3 mg/dL		Low	0 (0%)	0 (0%)	0 (0%)	5 (3%)	0 (0%)	1 (<1%)
		Normal	3 (1%)	3 (2%)	185 (89%)	172 (8%)	7 (3%)	3 (2%)
		High	0 (0%)	0 (0%)	3 (1%)	7 (4%)	11 (5%)	5 (3%)

For the UT-15 group, 14/16 those with high LDH at baseline, normalized at the end of 12-weeks. For the vehicle group 10/21 subjects had their LDH normalized. Among those with normal or low LDH at baseline for the UT-15 group, 15/180 subjects had low LDH at 12-weeks. For the vehicle group among those with low or normal LDH at baseline, 6/188 subjects had low values.

With respect to SGOT, the only notable observation is that among the 25 subjects with high SGOT at baseline 15 were in the low or normal range at the end of the study. For the vehicle group among the 30 subjects with high SGOT at baseline, 12/30 subjects were either in the low or normal range at the end of 12 weeks.

Total bilirubin, particularly, those with high values at baseline were normalized at 12 weeks with UT-15 treatment.

With respect to BUN and creatinine, the decrease in group means at 12 weeks seems to be related the number of subjects with high baseline measurements who normalize.

Specific subjects with abnormal values at end of treatment that this reviewer would find of concern (the sponsor lists approximately 700 line listings of subjects who had values outside the normal range for a given laboratory at either/or baseline and 12 weeks. This reviewer has listed in Table 89 several of the more extreme values at end of study.)

[107] *Adapted from Sponsor's Table 14.3.5.3A.*

Table 89. Outlier subjects for clinical chemistry (P01:04-05)

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
SGOT	04/6001	40	78	04/4003	26	105
	04/9019	20	60	05/50005	24	79
	05/7502	15	48			
SGPT	04/6001	40	86	05/53019	38	91
	04/9019	18	62	04/9002	8	55
	05/50001	159	185	05/59011	NA	73
	05/22504	18	87			
Albumin	04/7006	3.3	2.5	04/2022	3.4	2.8
	04/20007	3.1	2.5	05/52003	4.4	5.4
Alk phosphatase				04/9002	194	455
				05/59014	380	454
Calcium	04/2017	9.2	8.3	04/4011	9.3	10.5
	04/6002	9.4	7.3	04/7008	8.3	7.9
	04/20010	8.6	8.2	04/10022	9.1	8.0
	05/24506	9.6	10.5	04/20002	8.4	7.8
	05/51004	9.1	7.8	05/4505	9.4	8.2
	05/54013	8.7	7.9	05/19503	9.3	8.3
	05/56003	8.4	11.2	05/51005	8.8	7.0
	05/57001	9.1	7.6	05/52003	9.4	10.5
	05/59013	8.9	8.3	05/54023	8.9	8.3
	05/65001	9.2	8.2	05/53011	8.0	7.8
				05/58010	9.2	7.7
				05/59006	9.0	8.0
				05/61006	9.2	7.2
				05/64005	9.2	8.3
				05/65009	8.5	8.1
				05/66002	8.8	8.1
Creatinine	04/5005	0.9	1.3	04/3012	1.3	3.4
	04/10007	0.8	1.8	04/10006	1.7	2.9
	05/51004	1.3	1.6			
LDH	04/6001	225	447	04/10021	230	355
	04/12003	336	442	05/2501	276	372
	04/21004	NA	443			
	05/16502	248	532			
	05/50024	229	478			
	05/54027	216	402			
	05/60014	NA	463			
Bicarbonate	04/6002	27.7	15.1	04/3013	26.5	33.0
	04/19002	20.0	15.3	04/14002	NA	31.5
	05/16502	21.3	35.5	05/2501	22.9	16.2
	05/22504	26.3	33.3	05/53009	19.1	14.5
	05/50004	32.0	34.8	05/60008	19.3	16.6
	05/50020	NA	16.2	05/61006	19.6	14.5
	05/51002	20.0	14.8	05/64001	18.7	15.4
	05/65014	19.4	14.1			
Chloride	04/8010	109	116	04/10006	97	88
	05/16502	109	81	05/54014	96	83
	05/56003	107	92	05/61006	106	83
Potassium	04/3005	4.5	5.7	04/4016	3.3	2.7
	04/10005	4.4	3.2	04/2021	3.7	3.3
	04/20006	4.0	3.2	04/4016	3.3	2.7
	05/54028	NA	5.9	04/4018	3.5	2.2
	05/16502	4.5	3.1	04/8004	4.5	3.3
				04/10020	3.9	2.6
				04/12001	4.3	3.2

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
				04/19007	3.7	2.8
				05/52004	4.0	3.1
Sodium	04/2011	146	131	04/10006	134	127
	05/50014	125	117	05/61006	141	112
Bilirubin	04/5005	0.5	1.4	05/6009	2.1	3.7
	04/5011	1.1	1.7	04/23001	0.7	1.3
	04/7002	0.4	1.9			
	04/7005	1.6	2.3			
	04/7006	1.0	1.6			
	04/10015	2.5	3.5			
	04/14011	0.5	1.5			
	04/14007	1.4	2.3			
	05/4502	1.8	2.4			
	05/17502	0.6	1.3			
	05/17502	1.1	2.2			
	05/50011	NA	3.1			
	05/50019	1.2	2.5			
	05/50020	NA	2.3			
	05/53008	2.9	3.3			
	05/53017	1.5	2.8			
	05/60011	0.8	2.0			
	05/60012	0.9	1.6			
	05/61010	0.6	1.3			
	05/61002	1.4	2.3			
	05/61008	1.4	2.4			
	05/61012	1.2	2.0			
	05/65015	1.2	1.9			
	05/66003	2.1	2.9			
BUN	04/10009	22	43	04/3012	22	80
	04/22007	39	45	04/10006	65	135
	05/51004	20	40			

There appear to be more subjects in the UT-15 group whose calcium decreased by a substantial amount or was outside the normal range than for the vehicle group.

As the group means and shift tables would suggest more vehicle subjects had elevated bilirubin and LDH than UT-15 treated subjects.

Two UT-15 treated subjects had substantial increases in creatinine. The largest increase was from 1.3 to 3.4 mg/dL.

There were more subjects with substantial drops in K+ among those treated with UT-15.

Hematology

Serious adverse events associated with hematologic parameters. Several subjects had serious adverse events associated with altered hematology. Those subjects whose adverse events are associated with bleeding, whether the hematologic parameters were abnormal are also included. Any interpretation is confounded by the concurrent anti-coagulation that may predispose to bleeding as well as the asymmetry in the need for anti-inflammatory drugs that might also lead to bleeding.

UT-15

#04/5003- hospitalized for diarrhea, rectal bleeding and vomiting.

#04/5009- hospitalized with a right groin hematoma shortly after catheterization.

#04/ 7004- hospitalized several times for hemoptysis.

#04/9002- hospitalized for pancytopenia, (hemoglobin 8.9 g/dl; platelets 44,000/uL; WBC 3,740/uL). She recovered and completed.

#04/14009- Subject was admitted for anemia (hemoglobin 7.3 g/dL). The sponsor attributed the fall in hemoglobin to heavy menstrual bleeding. The INR at the time of the event was 1.43.

#05/14501- for an episode of hemolytic anemia.

#05/53020: This subject had an episode of melena. The INR was 4.9 the hemoglobin was 4.9 g/dL.

#05/58001- hospitalized due to hemoptysis and weakness.

#05/59003- hospitalized due to melena and marked asthenia.

#05/60005- hospitalized with a low platelet count (68,000) and low hemoglobin (9.6g/dL) associated with a high reticulocyte count (29%).

#05/65006- hospitalized for bleeding at the infusion site.

Vehicle

#04/10001- hospitalized for respiratory distress and hematemesis.

#04/20006- hospitalized for palpitations and prolonged menorrhagia.

#05/52004- epistaxis and anemia.

#05/60006- hospitalized for hemoptysis.

#05/60013- hospitalized for pneumonia. The WBC count was 17,000/L.

#05/64003- hospitalized because of hemoptysis.

Hematologic/bleeding events that were considered as adverse events are shown in Table 90.

Table 90. Hematologic adverse events (P01:04-05)

	Vehicle	UT-15
Injection site hemorrhage	0	2 #50021; #57002
Hemorrhage	13 #20010; #54002; #54003; #54006; #54016; #54024; #54026; #54028; #9018; #52007; #54007; #54025; #17501	7 #52004; #54018; #10020; #19003; #19005; #20005; #20002
Embolus	0	1 #9006
Melena	0	5 #03012; #10002; #53010; #58006; #53020
Rectal hemorrhage	0	3 #03012; #19502; #05003
Gastrointestinal hemorrhage	0	2 #09006; #59003
Gum hemorrhage	0	2 #20005; #65013
Hemorrhagic gastritis	0	2 #53010; #53020
Hematemesis	0	1 #5003
Bloody diarrhea	1 #20001	0
Ecchymosis	27 #01001; #04002; #04004; #04005; #04006; #5007; #6002; #20001; #20004; #20006; #20007; #20008; #20010; #20503; #08006; #14003; #50001; #500020; #65001; #65002; #65005; #65007; #65008; #65011; #65015; #66001; #4001	9 #20005; #20501; #65003; #20504; #65009; #65013; #04012; #20002; #20009
Anemia	3 #17502; #52006; #20006	3 #58006; #14009; #52004
Petechia	2 #20004; #20008	2 #20002; #20005
Hemolytic anemia	0	2 #60005; #14501
Purpura	0	2 #60009; #60005
Thrombocytopenia	0	2 #19503; #20502
Eosinophilia	0	1 #60010
Pancytopenia	0	1 #9002
Coagulation time increased	1 #9012	0
Hypochromic anemia	1 #54024	0
Myeloma	1 # 50011	0
Cerebral hemorrhage	0	1 #9006
Cerebrovascular accident	0	1 #12002
Hemoptysis	5	4

	Vehicle	UT-15
	#50013; #60006; #61008; #60013; #64003	# 20005; #20504; #58001; #07004
Epistaxis	4 # 20003; #22006; #61007; #61010	10 #2004; # 2012; #15007; #15501; #23003; #53022; #0312; #22005; #54004; #52004

Table 91. Selected hematology findings (P01:04-05)[108]

Parameter Norm range		Baseline		Week 12 change		
		Veh	UT-15	Veh	UT-15	P-value
Hemoglobin 11.2-18.1 g/dL	N x±SE	220 15±0.2	224 15±0.1	200 0.02±0.09	188 -0.46±0.09	<0.0001
Hematocrit 34%-54%	N x±SE	218 47±0.5	224 47±0.5	198 -0.1±0.3	188 -1.7±0.3	0.0002
Platelet count 130-400 /nL)	N x±SE	213 210±5	217 206±5	194 0.9±2.8	178 13.6±3.3	0.0007
WBC count 3.8-13.62 /nL	N x±SE	220 7.5±0.2	224 7.7±0.2	200 0.3±0.1	188 -0.2±0.1	0.027
Eosinophil count 0-6.8%	N x±SE	220 1.3±0.08	224 1.4±0.1	200 0.17±0.08	188 0.36±0.09	0.046

There were statistically significant drops in hemoglobin, hematocrit and WBC in the UT-15 group relative to vehicle. Neither lymphocytes nor neutrophil percentages significantly changed. Eosinophils were increased (data not shown). Platelet counts were increased.

The baseline hemoglobin/hematocrit values at baseline are particularly high for a predominantly female population. Not infrequently, subjects had baseline hemoglobin greater than 17 and hematocrit greater than 55. The high baseline value might reflect a secondary polycythemia in response to chronic hypoxia. In actuality, a greater fraction of the vehicle subjects had a shift from high to normal or low for hemoglobin than UT-15 subjects. For hematocrits an equivalent number of subjects whose value was high at baseline shifted to normal or low for both groups.

The shift table for hematologic values are shown in Table 92.

[108] *Derived from sponsor's Tables 14..3..5..5 to 14.3.5.6 (A-C) Mean ± SE at baseline end of treatment and change from baseline. P -values from Wilcoxon rank statistic comparing UT-15 to Vehicle. using rank changes scores.*

Table 92. Selected hematology shifts (P01:04-05)[109]

			Week 12					
			Low		Normal		High	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
Hemoglobin 1.2-18.1 g/dL	Baseline	Low	3(10%)	3 (2%)	6 (3%)	7 (4%)	1 (<1%)	2 (1%)
		Normal	8 (4%)	5 (3%)	164 (79%)	164 (84%)	8 (4%)	2 (1%)
		High	0 (1%)	0 (0%)	7 (3%)	6 (3%)	12 (6%)	27(4%)
Hematocrit 34-54%		Low	1 (<1 %)	2 (1%)	7 (3%)	6 (3%)	1 (<1%)	2 (1%)
		Normal	6 (3%)	4 (2%)	163 (78%)	156 (80%)	8 (4%)	3 (2%)
		High	2 (1%)	1 (>1%)	8 (4%)	10 (5%)	13 (6%)	12 (6%)
Platelet count 130-400 /nL)		Low	17 (8%)	19 (10%)	15 (7%)	21 (10%)	0 (0%)	0 (0%)
		Normal	10 (5%)	6 (3%)	162 (78%)	144 (74%)	2 (11%)	2 (1%)
		High	0 (0%)	0 (0%)	3 (1%)	1 (< 1%)	0 (18%)	3 (2%)
WBC count (3.8-13.6 /nL)		Low	3 (1%)	4 (2%)	4 (2%)	9 (5%)	0 (0%)	0 (0%)
		Normal	10 (5%)	1 (<1%)	190 (91%)	177 (90%)	1 (<1%)	1 (<1%)
		High	0(0%)	0 (0%)	0 (0%)	3 (2%)	1 (<1%)	1 (<1%)
Eosinophils 0-6.8%		Low	1 (<1%)	0 (0%)	5 (2%)	7 (4%)	0 (0%)	0 (0%)
		Normal	8 (4%)	1 (<1%)	182 (87%)	184 (94%)	4 (2%)	3 (2%)
		High	0 (0%)	0 (0%)	7 (3%)	0 (0%)	2 (1%)	1 (<1%)

Specific values that were marked changes are shown in Table 93.

[109] *Adapted from Sponsor's Table 14.3.5.7A.*

Table 93. Outlier subjects for hematology findings (P01:04-05)

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
Hematocrit	04/2013	46	55	04/2008	53	63
Change >±6	04/2017	50	40	04/2012	39	46
	04/5005	45	52	04/2022	43	37
	04/5010	53	44	04/3012	39	33
	04/7007	52	45	04/4003	52	44
	04/7010	55	46	04/7004	74	64
	04/9011	45	52	04/9002	31	44
	04/10007	41	34	04/9013	41	49
	04/14008	40	50	04/12002	47	54
	04/16001	33	40	04/14006	55	46
	04/20006	35	43	04/15001	52	45
	04/20007	52	45	04/16008	53	46
	05/7503	40	48	04/20009	57	50
	05/22504	38	45	04/22004	40	33
	05/24506	50	60	04/23001	42	52
	05/52007	64	53	05/12502	48	41
	05/54022	50	43	05/53009	67	56
	05/54025	42	49	05/53010	36	50
	05/54028	42	34	05/53011	69	51
	05/56003	35	44	05/53012	58	47
	05/57004	49	42	05/54001	44	37
	05/60012	60	51	05/54023	45	33
	05/61001	55	39	05/58009	76	64
	05/65001	52	44	05/58010	58	43
				05/59003	51	37
				05/59006	51	41
				05/64002	46	39
				05/66002	54	44
				05/66004	45	38
Hemoglobin	04/2013	15.9	17.6	04/2008	17.2	19.5
Change >±1.5	04/2017	15.3	13.1	04/2022	12.9	11.3
	04/4005	18.1	15.6	04/4003	16.6	14.0
	04/5010	15.9	13.7	04/4007	12.8	14.6
	04/7010	18.2	15.7	04/4012	22.8	20.1
	04/9003	12.9	14.8	04/4013	14.2	12.7
	04/9019	15.0	17.9	04/4018	16.0	13.6
	04/10007	13.6	10.2	04/7004	20.3	17.7
	04/10023	13.5	16.3	04/8002	17.4	15.5
	04/14008	12.1	16.1	04/9002	9.1	13.4
	04/16001	10.3	15.4	04/9010	14.7	11.9
	04/17001	18.9	16.4	04/9017	15.7	13.7
	04/20006	10.8	14.9	04/10021	16.2	18.3
	04/20007	14.8	13.1	04/10022	18.3	16.6
	05/5502	16.4	14.3	04/14006	17.1	15.2
	05/7503	13.8	15.5	04/15007	14.0	16.6
	05/16501	16.7	15.1	04/19003	15.2	13.5
	05/17502	11.8	10.1	04/22004	13.6	10.8
	05/22501	15.7	13.5	04/23001	13.3	17.1
	05/22504	12.9	14.8	05/12502	16.3	14.5
	05/24504	13.9	15.7	05/52004	14.2	11.5
	05/24506	16.7	19.4	05/53009	21.6	17.8
	05/50001	14.8	15.8	05/53010	11.8	15.8
	05/50019	17.4	19.4	05/53011	18.6	15.6
	05/51001	13.1	14.9	05/53012	18.4	16.8
	05/51002	13.9	16.0	05/54001	14.5	12.6
	05/52007	19.6	17.9	05/54004	20.6	18.1
	05/53006	12.8	14.7	05/54018	18.3	16.1

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
	05/54025	12.8	14.7	05/54023	15.3	11.9
	05/54028	13.6	11.2	05/58008	15.2	18.0
	05/56003	12.6	14.7	05/58010	16.5	14.2
	05/57003	18.8	20.4	05/59003	16.8	12.4
	05/57004	15.0	13.0	05/61005	16.8	15.1
	05/60012	17.8	15.2	05/64002	15.7	13.6
	05/61008	14.7	16.6	05/64005	17.2	15.1
	05/61012	18.1	16.4	05/65006	13.6	11.0
	05/65001	16.7	14.8	08/65002	15.8	13.4
	05/65005	12.1	10.5			
	05/65010	12.0	9.8			
	05/65012	14.9	16.6			
	05/65014	16.7	14.8			
	05/65015	17.0	15.4			
Platelets	04/10019	122	89	04/2022	105	213
Change >±75/nL	04/14001	180	107	04/4008	255	331
	04/17007	182	259	04/8004	309	173
	04/19006	117	79	04/9002	120	200
	04/21004	204	280	04/9010	166	89
	05/8501	432	348	04/10013	221	299
	05/10505	456	323	04/12004	270	351
	05/53015	195	273	04/20005	93	66
	05/54002	421	304	05/2501	296	209
	05/56003	207	111	05/9501	196	287
	05/60004	176	269	05/19504	283	359
	05/60013	214	136	05/20502	58	107
	05/60014	109	208	05/21501	360	269
	05/66006	274	190	05/22502	217	372
				05/24505	464	274
				05/53010	336	201
				05/59006	107	86
				05/60010	231	344
				05/64002	248	3540
Neutrophil count	04/10027	2.52	0.34	05/20502	NA	0.17
Change >±25%	05/20505	0.97	0.73	05/60008	1.39	1.07

Coagulation

Coagulation measures were collected on the CRF at baseline and week 12. . The results are not easily interpretable with respect to any kinetic interaction between UT-15 and warfarin. Changes in anti-coagulation (including other medications aside from warfarin) were allowed during the course of the study. Undoubtedly, coagulation measurements were required in response to the frequent changes in anticoagulation medications but these measurements were not captured on the CRFs. Of note is that most subjects in this study were inadequately anticoagulated. The prespecified goal was to have INRs between 1.5 to 2.5 among those receiving anticoagulation. Median values at the end of the study were 1.3 for the pooled studies. Subjects in study P01:05 were more likely than those in P01:04 to have INRs in the proposed range.

Table 94. INR data (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Baseline	N	106	112	104	102	210	214
	Median	1.2	1.2	1.5	1.3	1.2	1.2
	25th -75th %ile	1.0-1.4	1.1-1.4	1.1-2.2	1.1-2.1	1.1-1.7	1.1-1.5
Week 12	N	96	95	100	92	196	187
	Change	1.2	1.2	1.6	1.4	1.3	1.2
	25th -75th %ile	1.1-1.4	1.1-1.4	1.2-2.5	1.1-2.0	1.1-1.8	1.1-1.7

Urinalysis

Table 95 contains those who had findings on urinalysis in comparing baseline and week 12 for UT-15 and vehicle. There were more subjects with urinalysis abnormalities in the vehicle group than in the UT-15 group at baseline. The number of subjects with blood in the urine of +1 to +3 in magnitude, decreased in the UT-15 group. The effect was marginal in the vehicle group. There was also a decrease in subjects with +3 protein in the urine for 16 to 9 in the UT-15 group. Overall the number of subjects with any degree of proteinuria was the same for the UT-15 group, comparing baseline to week 12.

Table 95. Selected urinalysis results (P01:04-05)

		Baseline		Week 12	
		Veh	UT-15	Veh	UT-15
Blood	Trace	12 (5%)	6 (3%)	18 (8%)	13 (6%)
	1+	19 (8%)	12 (5%)	12 (5%)	9 (4%)
	2+	7 (3%)	7 (3%)	6 (3%)	2 (1%)
	3+	5 (2%)	7 (3%)	8 (3%)	3 (1%)
Protein	Trace	28 (12%)	23 (10%)	24 (10%)	22 (9%)
	1+	30 (13%)	17 (7%)	16 (7%)	21 (9%)
	2+	22 (9%)	17 (7%)	18 (8%)	20 (9%)
	3+	8 (3%)	16 (7%)	11 (5)%	9 (4%)

ECG

ECGs were performed at baseline and at the end of week 12. The specifics of the ECGs are summarized in Table 96.

Table 96. ECG data (P01:04-05)[110]

		Baseline		Week 12	
		Veh	**UT-15**	**Veh**	**UT-15**
ECG status	Unknown	6	6	42	26
	Normal	8	2	5	6
	Abnormal	219	228	189	201
Evaluable ECGs	N	227	230	207	194
	QTc >440 ms	78 (34%)	100 (43%)	89 (43%)	98 (51%)
	QRS >100 ms	63 (28%)	66 (29%)	68 (33%)	67 (35%)
	PR >200 ms	19 (8%)	18 (8%)	22 (11%)	33 (17%)
	Right axis deviation[111]	126 (56%)	154 (67%)	149 (72%)	156 (80%)
	Right atrial enlarge	37 (16%)	39 (17%)	35 (17%)	35 (18%)
	Right ventricular	38 (17%)	54(23%)	44 (21%)	42 (22%)
	hypertrophy	11 (5%)	13(6%)	15 (7%)	18 (9%)
	ST/T-wave abnormal	--------	--------	6 (3%)	6(3%)
	Nonspecific ST-T wave			1 (<1%)	1 (<1%)
	Specific ST depression			3 (1%)	0 (0%)
	Normal to abnormal			1 (<1%)	4 (2%)
	Abnormal to normal				
Intervals	Heart rate	80±14	81±14	80±14	82±13
Mean±SD	Change			0±11	1±12
	PR interval	175±32	171±29	171±32	169±30
	Change			-2±21	-3±27
	QRS	98±30	98±32	101±45	98±23
	Change			3±34	0±29
	QT interval	382±48	376±50	383±46	372±49
	Change			1±43	-5±49
	QTc	438±43	433±50	438±47	433±49
	Change			2±47	0±54

Comparing UT-15 to vehicle there did not appear to any differences in the effect in ECG abnormalities or intervals.

A.4.4.9 Summary

This review consists of a description of the protocol and the results of studies P01:04 and P01:05. The procedures and measurements for both studies were identical. These two studies are the pivotal studies that are to support the approval of UT-15 for the treatment of pulmonary hypertension, whose etiology is either due to primary disease, collagen vascular disease or congenital left to right shunts. Although the individual and pooled studies are suggestive of an effect of UT-15, this reviewer does not feel that the results of the studies are sufficient by themselves to support approval.

Subjects who enrolled into these studies were symptomatic pulmonary hypertension subjects (NYHA Class II-IV), despite optimum concurrent therapies. The etiology of the pulmonary hypertension could be either primary disease or could be as consequence of either collagen vascular disease or left to right congenital shunts.

The primary end point of both studies was the change in walking distance from baseline at the end of week 12 in comparing UT-15 to vehicle infusion. For the pivotal analyses missing values for those who discontinued were imputed. Those who discontinued either because of death, deterioration or adverse events had the worse rank or value

[110] *Data derived from sponsor's tables 14.3.8.1A and 14.3.8.2A.*

[111] *QRS axis +90 to ±180°*

imputed. Those who discontinued due to adverse events had their last rank or their last walk-distance carried forward.

The primary method of analysis was a non-parametric analysis of the pooled studies. The composite of walking distance both studies was pre-specified as pivotal in the analysis. The composite of both studies was to be considered demonstrating a benefit for UT-15 if either both individual studies were by themselves significant at the p< 0.049 or if one study was significant (p< 0.049) and the pooled studies had a p-value of less than 0.01.

By the sponsor's own analysis the study by itself would not be considered successful. Neither of the studies demonstrated a p-value of < 0.049, although their analysis demonstrated a p-value of < 0.01 for the pooled studies. The magnitude of the change in median walking distance ranged from 2 meters in study P01:04 to 19 meters in study P01:05, or between< 1% to a 6% increase in baseline walking distance and a mean increase of approximately 3% for the pooled studies.

Dr Lawrence, the FDA statistician, makes a cogent set of arguments, that when a study pre-specifies as a success the composite of several outcomes, the concept of "being close" is open to an enormous amount of ambiguity. In the absence of fulfilling the prespecified criteria for success all that can be said is that the study did not succeed.

Not only did the sponsor's analysis not meet the pre-specified criteria for considering the studies a success, there was an inherent bias in the statistical approach employed in the analysis of the study. There was a clear imbalance in the number of subjects who discontinued for adverse events, with nearly all such subjects arising from those treated with UT-15. Nearly all such subjects who discontinued due to adverse events had infusion site pain/infusion site reaction as the reason for discontinuation.

There are several consequences that result from this algorithm for imputing data for discontinued subjects. First, those who discontinue due to adverse events could never subsequently die, deteriorate or receive transplant. This fraction of subjects, therefore, was shielded from the worst imputed outcome values possible in this study.

Second, since nearly all subjects who discontinued in the UT-15 group did so because of infusion site pain/ reaction. Since infusion site pain was ubiquitous in the UT-15 infused subjects, the possibility exists that the discontinuation subjects were suffering from infusion site pain in conjunction with a worsening of their disease status.

Third, the process of imputation presupposes the values at early times are reflective of the performance at the time of discontinuation. There are clearly subjects whose imputed value clearly does not reflect their status at the time of discontinuation. Subjects who discontinue for pain, whose discontinuation fell within the time-window of an exercise test and who did not undergo further walk testing, the imputed values could be disparate with their clinical status at the time of discontinuation.

In order to deal with the inherent biases due to the unequal rates of discontinuation adverse events, this reviewer requested three additional analyses. The first analysis added the outcomes of three UT-15 and two vehicle subjects who died or were transplanted during the 100-day window defined for the 12-weeks of the study. Since these outcomes are really not subjective, the inclusion of these subjects at least partly corrects for the imbalance among those who discontinue for adverse events. Including the worst outcome for these subjects alters the p-value of the pooled database to 0.02 and that for the individual studies to >0.1.

The second analysis includes those, as having a worse outcome, who discontinued for adverse events if Flolan was started within one month of discontinuation and within the window of the study. There were six additional subjects. Two subjects were started on Flolan either prior to or immediately upon discontinuation of UT-15. Two additional

subjects were started within two weeks of discontinuation of UT-15 and two within one month of discontinuation of UT-15 therapy. None of these subjects obviously required Flolan at baseline. The immediate use of Flolan upon discontinuation of UT-15 suggests that the subject's status had deteriorated to the point that an optional treatment at baseline became a treatment of choice. The p-values for the pooled and individual studies when treating those subjects started on Flolan within 1 month of discontinuing UT-15 also as worse outcomes shifts the p-value for the pooled studies to 0.082. For each of the individual studies the p value was > 0.2.

A third analysis also included all those who were treated with Flolan during the window of the study as worse outcomes. In addition, there was one subject whose status at the time of continuation appeared to be inconsistent with the imputed measurement from week 1. The value for this subject was exclude. The p-values for this analysis for the pooled data was >0.1. The p-values for each of the individual studies were >0.2.

The above three analyses presume that all subjects who discontinued UT-15 therapy and received Flolan did so because of the deterioration in their status. Some or all of these subjects, however, may have been started on Flolan because no other options were available. An alternate analysis, performed by the sponsor imposes a last rank value for all those who discontinued prematurely, even if the reason was death, deterioration or need for transplantation. This analysis removes one source of the bias against the placebo in that no subject received a worse outcome. This analysis is sponsor's analysis # 4 in this review. The p-value for the pooled studies was 0.011 and that for the individual studies was between 0.07-0.08.

In summary, the study did not succeed by the pre-specified criteria of success. Neither study P01:04 or P01:05 was by itself statistically significant by a method of analysis that biases results towards UT-15 treatment. Other treatments, particularly of those who discontinued for adverse events further diminish the positive nature of any results.

Since the primary outcome of the study did not succeed by the pre-specified criteria, supportive measures of efficacy are more difficult to interpret. Nevertheless, there is a suggestion from the supportive information that UT-15 may have some effect on symptoms of pulmonary hypertension. The supportive symptoms were collected only among those who completed the study. Those who discontinued for any reason did not have any values imputed. In addition, the supportive symptoms were administered by the treating physician who might have been aware, based on the nature of infusion site reaction the subject's treatment.

Subjects showed some improvement in the composite of sixteen signs and symptoms of pulmonary hypertension. The metric that was used was a composite of all these symptoms. Subjects were assigned a "+1" for symptoms present at baseline and absent after 12-weeks, and a "-1" for symptoms that went from absent to present. Symptoms that were present at baseline and present at end of study, or absent at baseline and absent at end of study were assigned a value of "0". The average net change for those who completed the study favored UT-15 by + 1 units. The specific symptoms that were improved or were less frequently worsened in the UT-15 group were dizziness, palpitations, orthopnea and chest pain. The most troublesome symptoms of pulmonary hypertension, dyspnea and fatigue did not appear to be differentially improved across groups.

A second metric that was prospectively collected as a supportive end-point was the dyspnea-fatigue index. This metric consists of three components with values ranging from 0-4. The three components are "magnitude of task", "magnitude of pace" and "functional impairment". The higher the value, the less symptomatic the subject. There was a net increase of approximately 1.4 units in the overall symptom score among those treated with UT-15, approximately equally divided among the three components of this metric.

The quality of life metric was the Minnesota living with heart failure questionnaire. This questionnaire consists of 21 questions and is divided in to 4 domains. This QOL questionnaire was validated among subjects with CHF and not pulmonary hypertension, though the questions and limitation are somewhat similar among groups. The questionnaire is often analyzed as a global and three subcategories, physical, economical and emotional dimension. This questionnaire was not apparently administered to all subjects. Overall there was no global signal for this questionnaire. The global QOL did not differ between the two treatments. The physical dimension, however, was statistically favored the UT-15 group.

Each subject was asked to rank his or her degree of breathlessness after each six-minute walk by the Borg-dyspnea scale. This metric ranged from 1-10. The higher numbers suggest greater degrees of shortness of breath. The exercise coordinator performed this task and consequently is more likely to have been shielded from telltale adverse events that would indicate the specific treatment. Both the pooled studies and each of the individual studies were highly significant in improvement ($p<0.01$) of this metric. The magnitude was approximately 0.8 units.

It does not appear that UT-15 altered the natural course of pulmonary hypertension. Deaths, hospitalizations, hospitalizations for cardiovascular reasons or need for new or increases in medications or need for inotropic or Flolan during the 12-week study did not apparently differ between the two treatments. These metrics, however, were not prespecified as end-points, but are often collected and may served as convincing endpoints of benefit.

There were a total of 19 subjects who died during the window of the study. Ten of these subjects were in the vehicle group and nine in the UT-15 group.

Hospitalizations were equivalent in both groups. There were 40 subjects who were hospitalized or had their hospitalizations prolonged among the vehicle group and 38 among the UT-15 group. Two of those hospitalized among those randomized to vehicle were hospitalized after accidentally crossed-over and while treated with UT-15. The investigators at the various study sites did not adjudicate cause-specific hospitalizations. This reviewer, based on the capsular summaries found 22 of those treated with UT-15 and 25 of those treated with vehicle had their hospitalizations prolonged or required hospitalization as a consequence of cardiovascular or pulmonary hypertension related.

Subjects who status deteriorates may require new medications or increase in doses of ongoing medications. A difference in the need to alter medications may suggest a benefit of a given treatment. For the purposes of this assessment the following drug classes were considered: loop diuretics, calcium channel blockers, vasodilators (including hydralazine, clonidine, nitrates), ACE inhibitors or angiotensin II blockers, oxygen, Flolan, pressors, steroids, digoxin, aldactone or non-loop diuretics.

There was no difference in the number of subjects who required Flolan or inotropic support. This reviewer counted 12 subjects in the UT-15 group and 10 in the vehicle group that required either Flolan or inotropes. There were an additional 3 subject, all in the vehicle group that received flolan early in the course of the study, that suggested the infusion was a provocative test for vascular responsiveness and not a treatment for disease decompensation. These three subjects were excluded from the above count.

Among those who completed the study, there was a modest improvement in catheterized hemodynamics. Right atrial pressures, pulmonary artery pressures (mean, systolic and diastolic) and pulmonary vascular resistance were decreased. Cardiac index, stroke index and mixed venous oxygenation were increased. The effect on

hemodynamics, though statistically significant is in general small and of uncertain consequence. For cardiac index the net change (assuming that the data for those measured is consistent with the whole group) there was a net increase of 7.6%. There was an approximately 5% (3 mm Hg) decrease in mean pulmonary artery pressure. There was an approximately 18% decrease in pulmonary vascular resistance. Changes in CI, PAPm or PVR did not convincingly correlate with any benefit. The only consistent hemodynamic parameter with a positive correlation was SVO_2.

Dosing was predicated on improving symptoms of pulmonary hypertension while minimizing excessive pharmacologic effect or infusion related adverse events. It is therefore not possible to define either the initial, optimal or an appropriate dose range of use for UT-15 based on the data from this study.

Despite nearly an order of magnitude increase in mean infusion rate, there was minimal increase in walking distance among those treated with UT-15. The observed differences more reflect a worsening of the distance walked by the vehicle group than by an improvement among those taking larger and larger infusions of UT-15. There was no randomized withdrawal to ascertain a persistent (or any) benefit of UT-15. In fact among the hand-full of subjects who discontinued UT-15 acutely, no evidence of rebound was described.

With respect to safety, the duration of exposure was 81 days for those in the UT-15 group and 83 days for those treated with vehicle. The number of deaths and hospitalizations were equivalent between the two treatments. More UT-15 treated subjects than vehicle subjects had adverse events listed as severe in intensity (62% versus 20%). The vast majority of the difference reflects the irritating effect of active drug infusion.

Two subjects in the UT-15 group had episodes of hemolytic anemia. One subject discontinued treatment and the other subject continued on a lower dose of therapy. One additional subject had pancytopenia that the sponsor attributed to previous cyclophosphamide treatment. She continued on therapy. It does not appear that UT-15 is causative of these events since two of the three subjects continued on therapy.

The most frequent adverse events among those treated with UT-15 were also related to the “skin and appendage” system (94% versus 67%). The most frequently reported events were “infusion site pain” or “infusion site reaction”, 85% and 83% of those enrolled, respectively, the corresponding numbers among those treated with vehicle were 27% and 27%, respectively. “Gastrointestinal” symptoms were more frequent in the UT-15 than vehicle group (45% versus 32%), predominantly “diarrhea” (25% versus 15%) and “nausea” (22% versus 18%). Adverse events associated with the “nervous” system were more frequent in the UT-15 group than vehicle (30% versus 22%), with the most common adverse event described as vasodilation (11% versus 5%). Adverse events associated with “Metabolic and Nutritional” system had more events in the UT-15 group than vehicle (20 versus 13 %). The most frequent increase was in edema (9% versus 3%).

“Chest pain” (9% versus 4%), “dyspnea” (8% versus 3%), “cough” (8% versus 3%); and “infusion site bleeding” (44% versus 34%) was more frequent in the vehicle group than in the UT-15 group.

With respect to laboratory and hematology, group mean difference existed for: total bilirubin, LDH, BUN, hemoglobin, hematocrit and white blood cell count were all decreased relative to vehicle group. Platelet counts were increased in UT-15 relative to vehicle. Hypokalemia was noted in five patients treated with UT-15 and none with vehicle.

ECG intervals did not apparently differ among groups.

Vital signs were poorly followed. Blood pressure was only recorded for the initial infusion day. The dose of UT-15, however, was very low and consequently allows no assurance that hemodynamics was not effected by credible infusion rates of UT-15. There were, however, 29 subjects treated with UT-15 who had their dose decreased for excessive pharmacologic effect, with no further description as to the specifics of the event.

A.5 Study P01:07: A bioavailability study of UT-15 administered subcutaneously versus intravenously in healthy volunteers.

A.5.1 Sites and investigators

P01:07 was conducted at a single site in the United States.

Table 97. Investigators (P01:07).

Site	Investigator
01	PPD Development, West Austin Texas

A.5.2 Background

Initial protocol submitted: N/A

Protocol amendments: None.

Subject enrollment: 6.4.99 to 6.24.99

A.5.3 Study design

This single-center, open-label, non-randomized Phase I trial examined the pharmacokinetics and safety of single IV doses of UT-15 administered either by IV or subcutaneous routes. Healthy volunteers were given the drug at a rate of 15 ng/kg/min IV or SQ for 150 minutes, during which time samples for pharmacokinetic assessment were obtained. The patients were also monitored for safety using serum chemistries, CBC, ECG monitoring and vital signs. The IV and SQ periods were separated by a 5 to 7-day washout period.

A.5.3.1 Objectives

To assess the safety pharmacokinetics of a single IV and SQ dose of UT-15 in healthy volunteers.

A.5.3.2 Number of subjects/ randomization

Fifteen patients were to be enrolled in the study.

A.5.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.5.3.4 Dosage/ administration

Healthy volunteers were given the drug at a rate of 15 ng/kg/min IV or SQ for 150 minutes.

A.5.3.5 Duration/ adjustment of therapy

Therapy was not adjusted for any individuals enrolled in the trial.

A.5.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.22.

A.5.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.5.4 Results

Fifteen patients (7 female, 8 male) were enrolled in the trial and completed the infusion of both IV and SQ UT-15.

A.5.4.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyenand Gobburu.

A.5.4.2 Safety

There were no deaths reported in the study, and no SAEs during the IV or SQ infusions. The most common AEs reported were dizziness and heachache, which were more common in the IV formulation than following the SQ formulation. Injection site pain was more common in the SQ dosing.

A.5.5 Summary

A.5.5.1 Efficacy summary

Study P01:07 studied the acute effects of IV and SQ UT-15 in normal volunteers. No acute hemodynamic changes were detected for either formulation.

A.5.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other small trials of IV and SQ UT-15.

A.5.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

A.6 Study P01:08: A study to evaluate the effects of acetaminophen on the pharmacokinetics of UT-15 in healthy volunteers.

A.6.1 Sites and investigators

P01:08 was conducted at a single site in the United States.

Table 98. Investigators (P01:08).

Site	Investigator
01	T. Hunt, M.D., PPD Development, West Austin Texas

A.6.2 Background

Initial protocol submitted: N/A

Protocol amendments: None.

Subject enrollment: 8.3.99 to 9.20.99

A.6.3 Study design

This single-center, open-label, non-randomized Phase I trial examined the effect of acetominophen on the pharmacokinetics and safety of SQ UT-15. Healthy volunteers were administered UT-15, 15 ng/kg/min SQ for 6 hours in two dosing intervals separated by a 7 day washout period. In the first period, patients were given acetaminophen starting 25 hours before start of UT-15 and continuing through period of infusion.

A.6.3.1 Objectives

1. To assess the effect of oral acetominophen on the pharmacokinetics of SQ UT-15 in healthy volunteers.

A.6.3.2 Number of subjects/ randomization

Twenty-nine (29) patients were to be enrolled in the study and 26 completed.

A.6.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.6.3.4 Dosage/ administration

See trial design for details.

A.6.3.5 Duration/ adjustment of therapy

Therapy was not adjusted for any individuals enrolled in the trial. Two individuals were discontinued for drug-related reasons: one for pump failure (for SQ administration) and the other following vomiting of a dose of acetominophen.

A.6.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.22.

A.6.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.6.4 Results

Twenty-nine (29) patients, 17 females and 12 males, were to be enrolled in the study and 26 completed. One person withdrew consent, one discontinued for pump failure (for SQ administration) and the other following vomiting of a dose of acetominophen.

A.6.4.1 Efficacy

No efficacy data of clear relevance to the efficacy of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyen and Gobburu.

A.6.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions. The most common AEs reported were heachache (59%) and nausea (38%).

A.6.5 Summary

A.6.5.1 Efficacy summary

Study P01:08 studied the acute effects of acetominophen on the pharmacokinetics of UT-15. No acute hemodynamic changes were reported. The pharmacokinetics will be discussed in other reviews, but the sponsor reported no effect of acetaminophen on UT-15 pharmacokinetics.

A.6.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other small trials of SQ UT-15. The three discontinuations were unrelated to UT-15 adverse effects.

A.6.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

A.7 Study P01:09: A chronic, dose-escalation study of the pharmacokinetics of UT-15 administered by continuous subcutaneous infusion in healthy volunteers.

A.7.1 Sites and investigators

P01:09 was conducted at a single site in the United States.

Table 99. Investigators (P01:09).

Site	Investigator
01	T. Hunt, M.D., Ph.D. PPD Development, West Austin Texas

A.7.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 7.15.99 to 8.28.99

A.7.3 Study design

This single-center, open-label, non-randomized, dose-escalation Phase I trial examined the pharmacokinetics of UT-15 administered via SQ infusion for 28 days. Healthy volunteers received UT-15, starting at a dose of 2.5 ng/kg/min for 7 days. Doses were increased at 7 day intervals to 5, 10 and 15 ng/kg/min respectively for periods 2, 3 and 4. Serial plasma samples were collected for PK as well as clinical chemistries, CBC and coagulation parameters. Additional samples for PK were collected after discontinuation of UT-15.

A.7.3.1 Objectives

1. To assess the chronic pharmacokinetics of UT-15 administered by continuous 28-day SQ infusion.

2. To assess the safety and tolerability of chronic SQ UT-15 infusion in healthy volunteers.

A.7.3.2 Number of subjects/ randomization

Fourteen (14) patients were to be enrolled in the study. Six subjects completed the trial; 8 others discontinued due to infusion site pain.

A.7.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.7.3.4 Dosage/ administration

See trial design for details.

A.7.3.5 Duration/ adjustment of therapy

Dose of UT-15 was adjusted as detailed in the study design section above. Study lasted for 28 days.

A.7.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.22.

A.7.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.7.4 Results

Fourteen (14) patients were to be enrolled in the study. Six subjects completed the trial; 8 others discontinued due to infusion site pain.

A.7.4.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyenand Gobburu. The sponsor concluded that the trial demonstrated linear pharmacokinetics over the range of doses studied in the trial, with an apparent elimination half-life for the 15 ng/kg/min dose of 2.93 hours.

A.7.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions. The most common AEs reported were injection site pain (13/14 subjects), headache (11/14), nausea (7/14) and dizziness (7/14). Blood pressure and other vital signs did not change significantly from baseline in the patients. ECG evaluation did not find any significant changes from baseline.

A.7.5 Summary

A.7.5.1 Efficacy summary

Study P01:09 studied the pharmacokinetics of UT-15 during chronic SQ infusion. No hemodynamic changes during the 28 day study were seen. The pharmacokinetics will be discussed in other reviews.

A.7.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other long-term trials of UT-15, especially the prominent occurrence of site pain, which lead to the discontinuation of 8 of the 14 enrolled subjects.

A.7.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

A.8 Study P01:10: A single-center, open-label, mass balance, urinary metabolite profiling, and safety study of 14C-UT-15 following an 8-hour subcutaneous infusion in six normal healthy male subjects.

A.8.1 Sites and investigators

P01:10 was conducted at a single site in the United States.

Table 100. Investigators (P01:10).

Site	Investigator
01	Russell M. Dixon, M.D. Covance CRU, Madison WI

A.8.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 1.6.00 to 1.16.00

A.8.3 Study design

This single-center, open-label, non-randomized, Phase I trial examined the metabolic fate of 14C-labeled UT-15 in healthy male volunteers. Each subject received a single 8-hour infusion (SQ) of 14C-UT-15 at a rate of 15 ng/kg/min. Vital signs, clinical labs, ECGs and adverse events were monitored throughout the trial and at its conclusion.

A.8.3.1 Objectives

1. To characterize whole blood and plasma radioactivity of 14C-UT-15 following an 8-hour subcutaneous infusion in normal healthy male volunteers.

2. To characterize the urinary and fecal excretion of radioactivity following an 8-hour SQ infusion of UT-15.

3. To evaluate the safety of UT-15 under the same conditions.

4. To examine the pattern of urinary metabolites following the 8-hour SQ administration of UT-15.

A.8.3.2 Number of subjects/ randomization

Six patients were to be enrolled in the study. Six subjects completed the study.

A.8.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.8.3.4 Dosage/ administration

See trial design for details.

A.8.3.5 Duration/ adjustment of therapy

No adjustment of UT-15 dose was allowed.

A.8.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.23.

A.8.3.7 Statistical considerations

The statistics in the trial were observational in nature .

A.8.4 Results

All six enrolled subjects completed the trial.

A.8.4.1 Efficacy

No hemodynamic or symptom data related to the clinical effects of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyenand Gobburu. The majority of the radioactive label appeared in the urine (75.6% of dose). This radioactivity, analyzed by HPLC, corresponded to metabolic products of UT-15, including an oxidation product and a product formed through glucuronidation.

A.8.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions.

A.8.5 Summary

A.8.5.1 Efficacy summary

Study P01:10 studied the metabolism of UT-15 using radioactive labeling. These results will be discussed separately. No hemodynamic effects of UT-15 in the population were detected.

A.8.5.2 Safety summary

No deaths and no SAEs were reported. Adverse events related to drug administration were common but did not lead to drug discontinuation.

A.8.5.3 Reviewer's conclusions

No new safety concerns were identified in study P01:10. The pharmacokinetic results from this trial will be discussed separately by Drs. Nguyenand Gobburu.

A.9 Study P01:11: A multicenter, uncontrolled, open study in patients with pulmonary hypertension, transitioning from chronic intravenous flolan therapy to chronic subcutaneous uniprost.

A.9.1 Sites and investigators

P01:01 was conducted at 2 sites in the United States. The investigators are shown in Table 101.

Table 101. Investigators (P01:11).

Site	Investigator
01	Robyn Barst, MD
53	R. Naeije, MD

A.9.2 Background

Initial protocol submitted: 2.3.97

Protocol amendments: None.

Subject enrollment: 1.13.00 to ongoing (interim report as of 9.18.00).

A.9.3 Study design

This is an ongoing open-label protocol that allows for the transition of patients from Flolan to UT-15. The safety population at data cutoff for this submission consists of 3 patients and pharmacokinetic data on the use of subcutaneous UT-15 in pulmonary hypertension.

A.9.3.1 Objectives

1) To assess the safety of transitioning patients with pulmonary hypertension from Flolan to UT-15.

A.9.3.2 Number of subjects/ randomization

Three patients had been enrolled at the entry cut-off date for the interim report.

A.9.3.3 Inclusion/ exclusion criteria

Women and men receiving Flolan were eligible if they were able to give informed consent and could be trained in the use of the subcutaneous pump to administer the UT-15.

A.9.3.4 Dosage/ administration

Flolan were administered IV through a central venous catheter and UT-15 was administered subcutaneously.

A.9.3.5 Duration/ adjustment of therapy

Patients are eligible continue UT-15 for up to 36 months or until the drug approval.

A.9.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.62.

A.9.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.9.4 Results

Three patients only were enrolled in the trial, eliminating the utility of discussions of demographics, trial discontinuation, concomitant therapies, and standard safety analysis.

A.9.4.1 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nyugen and Gobburu.

A.9.4.2 Efficacy

No relevant efficacy data were obtained in this small study.

A.9.4.3 Safety

The three patients were taken off of Flolan and started on UT-15 for adverse events related to the use of a central venous catheter used for Flolan administration (sepsis, paradoxical cerebral emboli). The transition to UT-15 took place over 22 to 36 hours. Of the three patients enrolled, none of them were discontinued from UT-15 use for an adverse event during the available period of follow-up. The observed AEs were those reported in other larger trials included in the NDA 21-272: restlessness, headache and flushing. There were no deaths and no Serious Adverse Events reported during UT-15 administration during the follow-up for the three patients (followed for approximately one week, 6 months and 8 months respectively).

A.9.5 Summary

A.9.5.1 Efficacy summary

Study P01:11 is intended as an open-label study of the consequences of a switch from Flolan to UT-15. The three patients reported give minimal information in this regards, although all three were successfully transitioned, and have remained on UT-15.

A.9.5.2 Safety summary

No new safety concerns were identified in these three patients plausibly related to the initiation of UT-15 closely following the discontinuation of Flolan.

A.9.5.3 Reviewer's conclusions

This trial provides little information not available from other trials. The three patients were successfully transitioned to UT-15 from Flolan over a period of 22 to 36 hours.

A.10 Study P02:01: A pharmacokinetic study of subcutaneous 15AU81 (UT-15) in patients with secondary pulmonary hypertension: a study in patients with portopulmonary hypertension.

A.10.1 Sites and investigators

P02:01 was conducted at 7 sites in the United States. The investigators are shown in Table 102.

Table 102. Investigators (P02:01).

Site	Investigator
01	Sean Gaine, Univ. of Maryland, Baltimore
02	V. McLaughlin, Rush Presbyterian, Chicago
03	R. Oudiz, Harbor UCLA, Torrence
04	M. Krowka, Mayo Clinic, Rochester
05	D. Badesch, Univ. of Colorado
06	A. Frost, Baylor School of Medicine
07	R. Bourge, Univ. of Alabama Birmingham

A.10.2 Background

Initial protocol submitted: 9.12.97

Protocol amendments: None.

Subject enrollment: 1.20.98 to 10.15.98

A.10.3 Study design

This is a multi-center, open-label, baseline-control, single-dose study in subjects with portopulmonary hypertension with mild to moderate hepatic dysfunction.

A.10.3.1 Objectives

1) To measure the effects of subcutaneous 15AU81 on pulmonary and systemic hemodynamics in subjects with portopulmonary hypertension with mild to moderate hepatic dysfunction.

2) To characterize the pharmacokinetic profile of 15AU81 administered as a subcutaneous infusion in this patient population.

A.10.3.2 Number of subjects/ randomization

Twelve (12) patients were enrolled in the study.

A.10.3.3 Inclusion/ exclusion criteria

Inclusion Criteria:

1. At least 18 years of age;

2. If female, either surgically sterile, post-menopausal, or have a negative pregnancy test;

3. Have a diagnosis of severe, symptomatic pulmonary hypertension, NYHA Class II or III despite the use of oral vasodilators for at least one month;

4. Have pulmonary function tests c/w pulmonary hypertension, with only mild reductions in total lung capacity and forced vital capacity or a high-resolution CT scan showing no interstitial disease;

5. Have an echocardiogram within the past year c/w pulmonary hypertension: evidence for right ventricular hypertrophy or dilation; evidence of normal left ventricular function; absence of mitral valve stenosis;

6. Have a cardiac catheterization c/w pulmonary hypertension: pulmonary artery pressure >25 mm Hg; PCWP or left end-diastolic pressure >15 mm Hg; absence of congenital heart disease, with the exception of patent foramen ovale;

7. Signed consent form.

Exclusion Criteria (Following must not be present):

1. New form of vasodilator, diuretic or digoxin within the past one month.

2. Any medication discontinued in the past two weeks;

3. Any disease know to cause secondary pulmonary hypertension other than portal hypertension (COPD, thromboembolic disease, collagen vascular disease, sickle cell anemia, mitral valve stenosis, HIV disease).

4. Currently using another investigational medication or have received one in the past 30 days.

5. Severe heart failure (NYHA class IV);

6. Severe hepatic dysfunction (Grade C on Pugh classification scale).

7. Taking medications known to affect hepatic enzymes (i.e., cimetidine, phenytoin, rifampin);

8. Be more than moderately obese or underweight (>30% above ideal body weight

A.10.3.4 Dosage/ administration

UT-15 was administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes, or until an adverse event occurred which, in the opinion of the investigator, warranted discontinuation of the infusion. Following this, patients were followed for 300 minutes off UT-15 for adverse events.

15AU81 is constituted in a liquid at a concentration of 0.5 mg/ml. For a 70 kg man, the average rate of infusion will be 0.0014 ml/minute.

A.10.3.5 Duration/ adjustment of therapy

Patients were administered UT-15 for up to 150 minutes, or as tolerated by adverse events.

A.10.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.62.

A.10.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. The pharmacokinetic parameters of the patients were compared with the pharmacokinetics of healthy volunteers obtained in study P01:07. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.10.4 Results

Only nine patients enrolled, of the 12 proposed. All nine completed the 150 minute infusion of UT-15 with no reported deaths or SAEs during the infusion.

A.10.4.1 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nguyenand Gobburu.

A.10.4.2 Efficacy

No relevant hemodynamic efficacy data were obtained in this small study. The estimated half-life of UT-15 in this population was 1.3 to 1.4 hours, a value not different from healthy volunteers studied in P01:07.

A.10.4.3 Safety

All nine of the patients tolerated the 150 minute UT-15 infusion and the 300 minute washout period without reported SAEs. No deaths were reported during the study. The most commonly reported AEs were headache (78%), flushing (44%) and vomiting (22%). No significant changes in blood chemistries, urinalyses, CBC, vital signs or ECG compared with baseline were seen at 24 or 48 hours post-treatment.

A.10.5 Summary

A.10.5.1 Efficacy summary

Study P02:01 studied the effects of subcutaneous infusion of UT-15 in a population with porto-pulmonary hypertension. The study was too small for standard hemodynamic efficacy measures to be significant in the review of UT-15. The pharmacokinetic analyses will be examined elsewhere in the NDA review.

A.10.5.2 Safety summary

No new safety concerns were identified in this population. No evidence of rebound pulmonary hypertension was detected in the study, although the reported hemodynamic changes were minimal.

A.10.5.3 Reviewer's conclusions

This trial provides additional safety exposure in a population that differs from the population studied in the majority of the trials in the NDA. No new safety concerns were identified in the trial, although the small numbers of patients greatly limits the studies ability to detect such events.

A.11 Study P03:01: A dose range-finding pilot study of intravenous LRX-15 in patients with peripheral vascular disease: a study in patients with severe lower limb ischemia.

A.11.1 Sites and investigators

P03:01 was conducted at a single site in the United States.

Table 103. Investigators (P03:01).

Site	Investigator
01	Emile Mohler, Univ. of Pennsylvania, Philadelphia

A.11.2 Background

Initial protocol submitted: 12.23.97

Protocol amendments: None.

Subject enrollment: 3.30.98 to 10.01.98

A.11.3 Study design

This was a single-center, open-label, within-patient placebo-controlled sequential dose-escalation pilot study of LRX-15 (later renamed UT-15) administered as an intravenous infusion in subjects with severe lower limb ischemia. Subjects who meet the inclusion criteria, but none of the exclusion criteria, completed four phases: 1) a screening phase (days -7 to -1); 2) a baseline phase (study day 1); 3) a treatment phase (day 1); and 4) a post-treatment phase (days 1 to 3). During the treatment phase, subjects will receive: a) a dose-ranging segment, beginning with a 30-minute placebo infusion followed by escalating doses of UT-15 as tolerated; b) a maintenance segment, in which the subject will receive a 120-minute infusion of UT-15 at the maximum tolerated dose; and c) a washout period.

A.11.3.1 Objectives

1. To assess the safety, dose-tolerance and acute hemodynamic effects of subcutaneous 15AU81 in patients with portopulmonary hypertension with mild to moderate hepatic dysfunction.;

2. To characterize the pharmacokinetic profile of 15AU81 administered as a subcutaneous infusion in this patient population.

A.11.3.2 Number of subjects/ randomization

Eight patients were to be enrolled in the study.

A.11.3.3 Inclusion/ exclusion criteria

Inclusion Criteria (must be present):

1. Male or female, between the age of 40 and 75 years.

2. If female, either surgically sterile, post-menopausal, or have a negative pregnancy test;

3. Have a history of severe claudication confirmed by Doppler or other appropriate exam.

4. Have a diagnosis of Fontaine Stage III severe lower-limb ischemia; have an ankle:brachial index ≤0.5 (range 0.35 to 0.5); or toe pressure <30 mmHg; and be ambulatory.

5. Have an angiogram or MRI of the affected limb within 6 months of entering baseline consistent with 'severe ischemia.'

6. Able to sign an informed consent.

Exclusion Criteria (Following must not be present):

1. Prior history of:

a. bleeding disorder;

b. stroke or symptom of TIAs.

c. myocardial infarction, angina pectoris, or unstable angina or heart failure;

d. syncope.

2. An unstable concurrent medical condition.

3. Serum creatinine ≤ 2.5 mg/dl.

4. New therapy for PVD added within past one month.

5. Impaired liver function, defined as AST or ALT ≥2X upper limits of normal.

6. Have a toe ulcer on the ischemic leg.

7. Be hospitalized for limb-threatening ischemia.

8. Be receiving anticoagulants.

9. History of alcohol or drug dependence in past 3 months.

10. Be receiving an investigational agent, or having received one in the past 30 days.

A.11.3.4 Dosage/ administration

During the dose-ranging segment of the treatment phase, subjects will receive IV infusion of UT-15 for a minimum of 30 minutes for each dose in the following order: sterile citrate buffer (placebo), 10, 20, 40, 60, 80, 100, and 120 ng/kg/min UT-15. Dose escalation will continue until a clinically unacceptable change in hemodynamic parameters or vital signs is observed, or until other clinical signs or symptoms, including adverse experiences, are observed. The infusion rate immediately before the rate producing the unacceptable effect will be defined as the maximum tolerated dose for purposes of the maintenance phase.

Immediately following the dose-ranging phase, subjects will receive a 120-minutes infusion of UT-15 at the maximum tolerated dose. If any adverse clinical effects of UT-15 are noted during this period, the infusion rate of UT-15 is to be decreased or discontinued at the discretion of the investigator.

A.11.3.5 Duration/ adjustment of therapy

If any adverse clinical effects of UT-15 are noted during the constant infusion period, the infusion rate of UT-15 was to be decreased or discontinued at the discretion of the investigator.

A.11.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.63.

A.11.3.7 Statistical considerations

The statistics in the trial were observational in nature .

A.11.4 Results

Eight patients were enrolled in the trial and completed the dose-ranging portion of the study. Seven patients completed the 120-minute maintenance infusion at the maximum tolerated dose.

A.11.4.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. Per the sponsor, IV administration of UT-15 resulted in an increase in blood flow for the common femoral artery and anterior tibial artery.

A.11.4.2 Safety

The maximum tolerated dose of UT-15 was 10 ng/kg/min for 3 (38%), 15 ng/kg/min for one (13%), 20 ng/kg/min for three (38%) and 30 ng/kg/min for one (13%) patient.

There were no deaths reported in the study, and no SAEs during the initial infusion or the 120-minute maintenance infusion periods. The most common AEs reported were headache (88%) and vomiting (25%).

One patient discontinued during the maintenance phase due to headache and vomiting. There were no significant changes from baseline for clinical chemistry values, hematology, coagulation parameters, urinalyses, hemodynamic values or physical exam findings.

A.11.5 Summary

A.11.5.1 Efficacy summary

Study P03:01 studied the acute effects of IV UT-15 in patients with lower limb ischemia. None of the efficacy measures were relevant to the potential approvability of UT-15 for treatment of pulmonary hypertension.

A.11.5.2 Safety summary

No new safety concerns were identified in these patients plausibly related to the initiation of UT-15. The adverse events identified in this open-label study are similar to those reported in other small trials of IV UT-15.

A.11.5.3 Reviewer's conclusions

This trial provides little information not available from other trials. No new safety concerns were identified in this study

A.12 Study P76:01: A dose-range-finding study of intravenous 15AU81 in patients with congestive heart failure.

A.12.1 Sites and investigators

P01:01 was conducted at 3 sites in the United States. The investigators are shown in Table 104.

Table 104. Investigators (P76:01).

Investigator	Location
Kirkwood Adams, MD	Univ. of North Carolina
Mihai Gheorgiade, MD	Henry Ford Hospital, Detroit
Robert Bourge, MD	Univ. of Alabama at Birmingham

A.12.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 8.26.91 to 10.11.91

A.12.3 Study design

This multi-center, open-label study used a sequential dose-escalation design to assess the efficacy and safety of intravenous UT-15 in patients with symptomatic CHF (NYHA Class III or IV). Eligible patients underwent right-heart catheterization, followed by study drug administration:

1) Dose-ranging segment, when increasing doses of UT-15 were administered.

2) Dose-maintenance segment, when the maximum tolerated dose of UT-15 was administered for 90 minutes.

3) Wash-out phase lasting 90 minutes.

4) Post-treatment evaluation lasting approximately 24 hours.

Dose of UT-15 was adjusted/reduced per a protocol in the event of adverse effects.

A.12.3.1 Objectives

1) To assess the safety, dose-tolerance, and acute hemodynamic effects of UT-15 IV in patients with symptomatic heart failure.

2) To attempt to estimate the apparent half-life of UT-15 in the population.

A.12.3.2 Number of subjects/ randomization

Twelve (12) patients were enrolled in the trial, and 10 completed all of the study segments.

A.12.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- >28 years of age;
- Females must be post-menopausal or surgically sterile,
- had a diagnosis of severe, symptomatic heart failure (NYHA Class III or IV) at Screening/Baseline and for at least one month,
- LVEF ≤35%.

Exclusion criteria (may not be present)

- had a change in CHF therapy in the past 48 hours, including IV inotropes,
- systolic BP <80 mmHg or heart rate outside of 50-125 BPM.
- history of MI or resuscitated sudden death in past 3 months.
- History of v fib, unstable angina, or secondary cause of CHF (amyloid, thyroid disease, myocarditis).

A.12.3.4 Dosage/ administration

UT-15 was administered intravenously, with dose increased every 15 minutes in segment 1) as tolerated by the patients. The doses of UT-15 ranged between 5 and 120 ng/kg/min.

A.12.3.5 Duration/ adjustment of therapy

Study drug was administered in hospital, and where patients remained throughout the drug administration and for 24 hours thereafter.

A.12.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.62. Invasive hemodynamic, vital sign, and ECG monitoring made during the period of the infusions and at the end of the washout period along with pharmacokinetic sampling and routine vital signs. After washout, vital signs and ECGs, labs and adverse events were also measured at the time of discontinuation from the study (approximately 24 hours).

A.12.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. The pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.12.4 Results

A.12.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were men (11/12, 89%), with seven blacks and 5 whites. The mean age was 47 years old. The mean LVEF was 16±2%, and the right-ventricular EF was 35±1.8%. The reader is referred to the study report for additional demographics.

A.12.4.2 Disposition of subjects

Of the 12 patients enrolled, 2 patients were discontinued for severe hypotension. These are discussed in Safety below.

Subject selection. No information is available about subject selection in protocol P76:01.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. Given the short duration of the trial no concomitant medications were used during the administration of the study drug.

A.12.4.3 Pharmacokinetics analyses

The serum levels were below the threshold for their assay to detect, so no useful PK results exist.

A.12.4.4 Hemodynamic changes

The maximum tolerated dose of UT-15 IV varied between 10 and 60 ng/kg/min in the 10 patients who completed the study. The table below summarizes the hemodynamic changes in the trial, comparing the observed effects at the maximum tolerated dose

with the effects of the vehicle-only infusion. Acute effects of UT-15 on the measured parameters, including changes in PCWP and CO, trended in favor of UT-15.

Table 105. Change from baseline in hemodynamic parameters (P76:01)[112]

	Change from vehicle only to MTD[113]
HR (bpm)	+0.8±2.5
Right Atrial Press (mmHg)	-4.6±1.4
Cardiac Output	+1.7±0.4
Pulmonary Artery Press (mm Hg)	-9.7±2.5
PCWP	-3.5±1.6

A.12.4.5 Safety

None of the adverse events reported in the trial were 'serious' per the sponsor, although hypotension lead to the discontinuation of two patients. An additional patient had chest pain radiating to his left arm but continued in the trial.

The two patients discontinued for hypotension developed hypotension, headache, and restlessness that did not respond to reduction in the dose of UT-15.

Headache and restlessness were the two most commonly reported adverse events, occurring in 75% and 40% of the patients respectively.

A.12.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.12.4.5.2 Comments on specific safety parameters

Deaths. There were no deaths reported for subjects in the trial.

Serious adverse events. No SAEs occurred during the administration of study drug, but see note above regarding two patients with hypotension.

ECG changes. The sponsor reported that while baseline abnormalities existed in all ECGs at baseline, no changes in the ECGs between baseline and follow-up occurred.

A.12.5 Summary

A.12.5.1 Efficacy summary

Study P76:01 measured the acute hemodynamic effects of IV administration of UT-15 in patients with Class III/IV heart failure. The changes measured in this open-label trial were consistent with an acute effect of IV UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. No pharmacokinetic analyses were performed due to technical failure of the assay used to measure the UT-15 concentrations.

A.12.5.2 Safety summary

There were no new safety concerns identified in this small study, but the route of administration differ from the proposed route (IV not subcutaneous), as does the study population. Significant hypotension was seen in two patients given UT-15 in the trial, along with the usual adverse events of headache and restlessness.

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[112] *Data from NDA vol. 2.62, table 9a.*

[113] *Maximally tolerated dose.*

A.12.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of IV UT-15 to cause pulmonary vascular dilatation. No information about the relationship between dose of UT-15 and hemodynamic effects can be obtained from a trial of this design (open-label, dose-ascending). No new safety concerns emerged from the trial that are of particular relevance to the proposed subcutaneous use of UT-15.

Appendix B Response to Request for Information

On 20 November 2000, the FDA requested further information to support the classification of patients' discontinuation as due to an adverse event (infusion site pain) as opposed to clinical deterioration. Eighteen patients discontinued from Protocol P01:04/05 due to intolerable infusion site pain, as noted in NDA 21-272, Item 8, Study P01:04/05, Volume 2.34, Listing 16.2.1.6, page 6518. Narratives of these discontinuations were included in NDA 21-272, Item 8, Study P01:04/05, Volume 2.31, Table 14.3.4, page 5609.

The sponsor contacted each clinical center and discussed with study staff the clinical circumstances surrounding the patient discontinuation. Particular attention was given to why the patient was discontinued from the study and the patient's clinical status at the time of discontinuation. If Flolan was initiated, additional information was obtained describing the time course of, and reasons for its initiation. Patient status as of December 2000 was obtained. This information follows in brief narratives and is summarized in Table 1. In addition, individual patient data previously submitted in the NDA are listed in Table 2 including results of individual Six-Minute Walk tests and Dyspnea-Fatigue evaluations.

Patient 02001 was enrolled in the study for 43 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline, though dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study; however increased dyspnea on exertion was noted post-UT-15. Flolan therapy was initiated six weeks post-UT-15 for worsening pulmonary hypertension. The patient was alive as of December 2000.

Patient 02006 was enrolled in the study for 71 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated electively two weeks post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. The patient was alive as of December 2000.

Patient 02016 was enrolled in the study for 47 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient was improved during the study, but deteriorated with discontinuation of UT-15. The patient requested initiation of Flolan therapy four months post-UT-15 to replace the beneficial effect of UT-15. The patient was alive as of December 2000.

Patient 02020 was enrolled in the study for 38 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated electively at one-month post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue ratings remained unchanged. In the investigator's opinion the clinical status of this patient was improved during the study, but deteriorated with discontinuation of UT-15. The patient was alive as of December 2000.

Patient 05009 was enrolled in the study for 42 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. In the investigator's opinion the clinical status of this patient did not deteriorate during the study, though exercise and dyspnea-fatigue rating worsened compared to baseline. The patient was alive as of December 2000.

Patient 07004 was enrolled in the study for 25 days*[114] when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise improved and dyspnea-fatigue rating remained essentially stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 10507 was enrolled in the study for 9 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 or until transplantation two months post-UT-15; the patient was listed for transplantation prior to study enrollment. While receiving UT-15, dyspnea-fatigue rating remained essentially stable compared to baseline; other than the baseline exercise, no other exercise test was conducted. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 11002 was enrolled in the study for 31 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline though dyspnea-fatigue rating remained essentially stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Pulmonary hypertension symptoms worsened post-UT-15 leading to Flolan treatment two months later. The patient was alive as of December 2000.

Patient 11003 was enrolled in the study for 56 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Pulmonary hypertension symptoms worsened post-UT-15 leading to Flolan treatment three months later. The patient was alive as of December 2000.

Patient 14012 was enrolled in the study for 58 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise remained essentially stable with improvement in dyspnea-fatigue rating. In the investigator's opinion the clinical status of this patient was improved during the study; however increased dyspnea was noted after discontinuation of UT-15. The patient was alive as of December 2000.

Patient 19001 was enrolled in the study for 70 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan

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[114] NDA summary tables indicate patient 07004 was enrolled in the study for 87 days; however UT-15 was permanently discontinued on Day 25 as indicated above.

therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. In the investigator's opinion the clinical status of this patient was improved during the study though the dyspnea-fatigue rating worsened compared to baseline; a Week 6 exercise test was not performed. Flolan therapy was initiated two months post-UT-15 to replace the beneficial effect of UT-15. The patient was alive as of December 2000.

Patient 19005 was enrolled in the study for 69 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline though dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Flolan therapy was initiated five months post-UT-15 at a hospital outside of the clinical study. The patient was alive as of December 2000.

Patient 19008 was enrolled in the study for 45 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise was improved though dyspnea-fatigue rating was reduced modestly compared to baseline. In the investigator's opinion the patient's clinical status did not deteriorate during the study. The patient was alive as of December 2000.

Patient 19502 was enrolled in the study for 46 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated one-month post UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient improved during the study. Pulmonary hypertension symptoms worsened post UT-15 leading to Flolan therapy one month later. The patient was alive as of December 2000.

Patient 52008 was enrolled in the study for 37 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was initiated electively immediately following discontinuation of UT-15. While receiving UT-15, exercise was modestly improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate, but symptoms of pulmonary hypertension worsened post UT-15 while receiving Flolan. The patient underwent transplantation four months post-initiation of Flolan therapy. The patient was alive as of December 2000.

Patient 54011 was enrolled in the study for 31 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been initiated as of December 2000. While receiving UT-15, exercise was reduced though dyspnea-fatigue rating improved compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 54012 was enrolled in the study for 16 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not initiated immediately following discontinuation of UT-15, but was initiated electively within the first week post-UT-15. While receiving UT-15, exercise was improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 54018 enrolled in the study for 47 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. In anticipation of discontinuing UT-15, Flolan therapy was initiated electively one day prior to discontinuation of UT-15. While receiving UT-15, exercise and dyspnea-fatigue rating remained essentially stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

In summary, following additional communication with the study centers, the sponsor maintains that all 18 patients are properly categorized by the investigators as discontinuations due to an adverse event (infusion site pain); none of the patients in question were withdrawn due to clinical deterioration.

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Table 2
Listing of Information for Patients Who Discontinued Early
Reason for Discontinuation: AE

Trt	Pt	Etiology	NYHA	Day of Disc.	Max Dose	Date at Week 12	Death?	Flolan?	PVRI	CI	Six-Minute Walk Day	Six-Minute Walk Dist	DF Score Day	DF Score Score
Active	02001	Shunt	III	43	5.00	09FEB99	No	Yes:6w	33.2	1.7	1	479	1	6
											9	446	8	6
											43	132	43	6
	02006	CTD	III	71	2.50	15APR99	No	Yes:2w	38.1	1.1	1	388	1	6
											9	470	6	6
											43	495	43	6
	02016	Shunt	III	47	3.75	22JUN99	No	No	14.8	2.2	1	198	2	6
											5	406	5	6
	02020	PPH	III	38	3.00	21OCT99	No	Yes:4w	24.1	2.3	1	264	1	8
											9	347	9	8
	05009	Shunt	III	42	1.25	30SEP99	No	No	24.1	2.4	0	337	0	7
											9	253	9	3
											42	276	42	3
	07004	Shunt	II	87	1.50	18AUG99	No	No	54.8	2.8	0	345	1	7
											10	393	10	6
											44	Too Ill	45	7
											87	398	87	6
	10507	Shunt	IV	9	1.25	25JAN00	No	No			2	183	2	1

													9	3
11002	PPH	II	31	2.50	25MAY99	No	No	25.4	2.0	2	370	1	4
										9	381	9	4
										30	229	30	3
11003	Shunt	III	56	2.50	29SEP99	No	No			-11	287	1	2
										7	323	7	2
												36	2
14012	CTD	III	58	6.25	19NOV99	No	No	7.4	3.0	2	339	1	6
										9	345	9	6
										44	333	44	6
												58	9
19001	PPH	III	70	3.75	04FEB99	No	Yes:8w	23.5	2.0	1	383	1	6
										8	383	8	6
										41	ND	41	2
19005	PPH	III	69	5.00	04MAY99	No		26.2	1.7	1	264	1	5
										10	276	10	6
										45	180	45	6

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Table 2
Listing of Information for Patients Who Discontinued Early
Reason for Discontinuation: AE

Trt	Pt	Etiology	NYHA	Day of Disc.	Max Dose	Date at Week 12	Death?	Flolan?	PVRI	CI	Six-Minute Walk Day	Six-Minute Walk Dist	DF Score Day	DF Score Score
Active	19008	PPH	III	45	5.00	07SEP99	No	No	27.6	2.2	1	315	1	7
											12	343	10	5
											45	355	45	5
	19502	CTD	IV	46	1.30	18JAN00	No	Yes:4w	22.6	2.0	1	186	1	2
											8	207	8	4
											45	241	45	2
	52008	PPH	III	37	2.60	25JAN00	No	Yes:0d	29.8	1.5	2	260	2	2
											9	273	9	2
	54011	Shunt	III	31	2.50	11AUG99	No	No		2.5	2	288	0	3
											9	235	8	6
	54012	PPH	III	16	2.50	19AUG99	No	Yes:5d	41.3	1.2	1	233	1	3
											9	275	10	3
	54018	PPH	III	47	4.37	14SEP99	No	Yes:-1d	32.8	1.4	1	335	2	3
											10	380	11	3
											46	325	47	3